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BIOLOGICAL THERAPY

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BIOLOGICAL THERAPY

Volume 1

General Therapy

Physiological Therapy

Medical Therapy

Diagnosis

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[To the Medical Profession.]

BIOLOGICAL THERAPY

including

Vaccine Therapy

Serum Therapy

Phylacogen Therapy

Gland Therapy

Diagnostic

Proteins



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New editions of some of our larger booklets being required, we have decided to issue, for the convenience of the medical profession, a comprehensive volume under the title "Biological Therapy," combining those publications descriptive of remedies mainly obtained from bacterial and animal sources that have hitherto been issued separately. "Biological Therapy" therefore contains treatises on Vaccine Therapy, Serum Therapy, Phylacogen Therapy, and Gland Therapy, and full particulars of our Diagnostic Protein Extracts.

Part I. of the book (pages 1 to 94) consists of a new and enlarged edition of "Vaccine Therapy." The introduction (pages 1 to 23) has been written by Sir Almroth E. Wright, M.D., and the remainder of this section (pages 24 to 94) has been contributed by members of the staff of the Inoculation Department, St. Mary's Hospital, London. Our "Vaccine Therapy" has already passed through twelve editions, and has long been accepted as an authoritative exposition of this branch of therapeutics. The new edition contains more than double the matter of any previous issue, and coming direct from the fountain head of therapeutic inoculation is assured of a most cordial reception.

It seems hardly necessary to point out that the stock vaccines therein described are the same as those used in the Inoculation Department, St. Mary's Hospital, and thus, by constant observation of their effects on the patients, the standard of the vaccines is maintained at a high level. The proportion of the proceeds of the sale of these vaccines which accrues to the Inoculation Department, is applied to the upkeep of the in- and out-patient departments, and the laboratories of the Institute of Pathology and Research, St. Mary's Hospital.

Part II. (pages 95-186) deals with a variety of biological remedies of great interest, but of necessity in a more condensed manner. Serum Therapy is now thirty years old, and the main facts have long been current in medical literature.

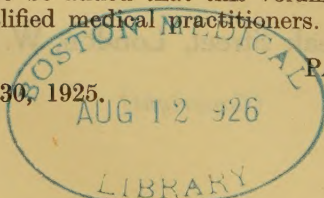
Of other subjects dealt with in this section Gland Therapy is the most important. Detailed descriptions are given of the therapeutics of thyroids, parathyroids, suprarenal substance (including Adrenalin), the pituitary (including Pituitrin and Antuitrin), and the ovaries (including ovarian substance, corpus luteum and ovarian residue). A considerable volume of clinical evidence has accumulated showing that these products possess definite activity. Regarding orchic substance, the placenta, the thymus, mammary and pineal glands, there is, at present, less to be said of a positive nature.

In the list of gland products will be found a few formulæ of compound tablets. No recommendations are offered with these, and physicians must themselves decide as to their applicability in any given case.

It only remains to be added that this volume is circulated exclusively amongst qualified medical practitioners.

London, June 30, 1925.

PARKE, DAVIS & Co.



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PART I.

VACCINE THERAPY.

INTRODUCTORY.

Vaccines have three separate uses. They serve : (a) for prophylaxis against zymotic diseases, (b) for the treatment of subsisting infections, and (c) for preventing their recurrence.

Mode of Action.—Vaccines act only indirectly upon microbes. They act as antigens, i.e., they engender in the organism antibodies which enter into destructive chemical combination with infecting microbes. In addition, vaccines would appear to augment the phagocytic activity of the leucocytes, and also to incite these cells to set free into the blood the ready made non-specific bactericidal substances which they contain.

Procedure Employed in the Preparation of Vaccines.—The bacterial vaccines considered below are prepared by growing the micro-organisms in pure culture, making suspensions of these, sterilising without overheating, standardising by enumeration of the contained microbes or, as the case may be, by weighing the dried bacterial powder ; and finally making the appropriate dilutions in carbolised salt solution. The efficacy of these vaccines is controlled by observing their effects on patients in the Research Wards and Out-Patient Clinics of the Inoculation Department of St. Mary's Hospital, London. In the case of some of the more important vaccines their efficacy is further tested by carrying out vaccine-response tests upon the blood *in vitro*. It is proposed gradually to extend this system.

Making, Standardising, and Testing the Efficacy of Vaccines : Indispensable Requirements and Desiderata.

Vaccines should be accurately standardised and tested for efficacy; in other words the amount of bacterial protoplasm or derivative antigen contained in the unit of volume should be indicated; vaccines which bear the same label should have exactly the same potency; and the antigen furnished should be of the most efficient quality.

There should be sent out with the vaccines information as to dosage, distinguishing between that applicable to (a) healthy men, (b) lightly, and (c) heavily infected patients.

1.—Vaccines should be Accurately Standardised and Information as to Dosage should in each Case be supplied.

Information with regard to dosage must in each case be supplied. The dosage for prophylactic inoculation must obviously be worked out beforehand. For the medical man who administers the vaccine has, except in time of epidemic, no clinical test which will tell him whether



the vaccine has done what was required of it. Again in the case where the vaccine is to be employed in the treatment of any acute or virulent infection the exact dose must be given. For it would be inadmissible to proceed in these cases simply by trial and error. Lastly, in cases of chronic localised cases where it is practicable to arrive at the proper dosage by trial and error, it will of course be desirable to start with a dose that will be approximately right.

Effort has not been spared to procure the information which is supplied under these several headings.

But it is of fundamental importance that the reader should realise (1) that the working out of the proper dose of a vaccine demands even in the simplest case—the case of prophylactic inoculation—very long and laborious research work ; (2) that the problem of arriving at the proper dosage is a problem still largely unsolved ; (3) that the determination of the proper dose of any vaccine should rank as an achievement far above an innovation in the processes of making a vaccine ; and (4) that if at any time one had to make a choice between the employment of a newer, theoretically superior, antigen, whose dosage had not been worked out, and the employment of a theoretically inferior vaccine of which the doses had been ascertained, one should unhesitatingly elect for the latter.

2.—The Antigen which is Supplied in the Vaccine should be the Most Efficient Possible Description of Antigen, and the Theoretical Considerations which Justify a Preference for the Particular Type of Vaccine which is Offered should be Adduced.

The requirement that the vaccine should supply the most efficient form of antigen is kept insistently before the medical profession and the public by the continual invention of new vaccines which are always expected to do things which are quite obviously impossibilities. It is therefore necessary to consider the position with regard to antigens. It was originally assumed that only vaccines consisting of living microbes could be efficacious. Later, it was ascertained that vaccines consisting of microbes killed by heat were perfectly potent, and this led directly to anti-typhoid inoculation. It was then further ascertained that cultures killed in a variety of different ways also furnish effective vaccines. And finally, it has recently been established that cultures which have been exposed to the severest chemical treatment, also all sorts of bacterial extractives, furnish antigens. It is in virtue of the establishment of these facts that the problem of choosing between all sorts of different vaccines has come up.

Inasmuch as the requiring of reasons operates as a check upon irrational conservatism on the one hand, and futile and mercenary innovation on the other, the practitioner should in each case enquire into the *a priori* reasoning which is held to warrant the assumption that the particular variety of vaccine offered is that which furnishes the best kind of antigen.

Further, the practitioner should in connexion with every vaccine require that its efficacy should have been established by practical tests. In particular, when the question of superseding one vaccine by another comes up, the practitioner should ask for evidence of the superiority of the newer vaccine, and, finally, he should, with regard to every new vaccine, stipulate that its dosage should have been worked out and published.

3.—How the Efficacy of a Vaccine can be Established.

The efficacy of a vaccine can be established :—

(a) By setting out records of the immunological responses produced when we inoculate the vaccine into a healthy man or, as the case may be, add it to his blood *in vitro*.

(b) By inoculating the vaccine prophylactically into man or animals—and then investigating the effects; in the case of man, by statistical enquiries, and in the case of animals, by testing with graduated doses of virulent living cultures. Statistical investigation is in practice applicable only to large bodies of men exposed to epidemic or endemic infections; and direct animal experimentation only to those microbic diseases which will kill laboratory animals.

(c) By employing the vaccine in the treatment of infections of animals or man, and appraising the results by comparing the condition of the patients before and after treatment, and observing the rate of recovery—using for such testing cases of which we can be confident that they will, if left untreated, run a protracted course and not take a dramatic turn for the better.

The superiority of one vaccine over another can be established only by showing that the one vaccine gives successful results in cases which the other fails to affect. But it will be well here to ponder carefully the legal maxim that “a discovery is a new manufacture of which the normal result is success.” For an occasional better clinical result obtained by changing over from one variety of vaccine to another may of course be due, not to the superior quality of the vaccine, but to the fact that a favouring fortune has put into the practitioner’s hands a dose which has better met the requirements of the patient.

4.—The Principles Enunciated above are Conformed to in the Case of the Vaccines here in Question.

(1) The requirement of standardisation is, in the manner explained above, duly satisfied.

(2) The *a priori* grounds for inferring that the type of vaccine here offered—the *plain sterilised and standardised bacterial suspension*—is that which is best calculated to furnish the required antigen, are as follows :—All artificial immunisation is modelled upon that acquired as a result of infection. The antigens which in natural circumstances bring about a cure and subsequent immunity are derived from the artificially unaltered bacterial protoplasm of microbes which have met their death in the organism. The more closely we imitate this effective

antigen the greater should be our prospect of success. And vaccines consisting of microbes which have been heated only up to their thermal death point would appear to imitate as closely as possible the antigen employed by nature.

(3) The efficacy of the vaccine is carefully tested.

(4) The requirement that the doses of vaccine for healthy men and for lightly and heavily infected patients shall be given, is also complied with.

PROPHYLACTIC EMPLOYMENT OF VACCINES.

I.—Prophylactic Inoculation against Zymotic Diseases of Bacterial Origin.

The simplest form of inoculation is that employed prophylactically against zymotic diseases :—typhoid fever, plague, Malta fever, cholera, epidemic pneumonia. But even here a number of only incompletely solved fundamental questions come up for consideration : —

The first is as to how nearly the strain of microbe which comes into application should be related to the microbe against which protection is sought.

The second is the question of how the optimum dosage for ordinary cases should be arrived at.

The third, that of the repetition and proper interspacing of the doses.

The fourth, that of the optimum dosage for inoculation conducted in the presence of infection.

1. Question as to how nearly the Microbe which comes into Application in the Vaccine should be related to the Microbe against which Protection is Sought.

This question can be formulated also differently. It can be framed thus :—Is a vaccine capable of conferring protection against microbes of a different strain or, as the case may be, species to that which has been employed in its manufacture ?

At the moment, this question may be dealt with only in general outline, the detailed discussion of the question of the comparative advantages of stock and autogenous vaccines being postponed till we come to deal with vaccine therapy (see page 10).

Let us begin with what is fundamental and obvious. Common sense will show that there can in prophylactic inoculation be no question of employing for the manufacture of the vaccine the particular strain of microbe which the patient will afterwards encounter. The best that can be done is to employ a stock vaccine prepared from a microbe belonging to the same species. And one can clearly see from a survey of the results obtained in practice that that suffices.

Prophylactic inoculation could not give the satisfactory results it does if vaccines did not, in addition to giving protection against the particular strain of microbe which furnished the vaccine, give protection

also against the various other strains which are abroad in the world. And it is notorious that vaccines give protection not only against the microbes of the vaccine's country of origin but also against those of all countries.

The question as to whether a vaccine must be made from a microbic strain precisely similar to that which is to be combated is, in accordance with this view, one which may unhesitatingly be answered in the negative.

This conclusion wins support also from the results obtained from immunological tests applied to the blood of patients prophylactically inoculated. To take a concrete example, the blood of persons inoculated with antityphoid vaccine agglutinates and kills in enormous numbers not only the strain of typhoid bacilli which has furnished the vaccinating material but also all other strains of typhoid bacilli.

A word of caution in connexion with the interpretation of blood tests may here be added. Certain of the blood tests are decisive, others indecisive. Those which take into consideration—as those employed in ordinary *typing* experiments do—only agglutinating power, are fallacious. It should be remembered that agglutinins attack only a subsidiary and very specialised constituent of the bacterial protoplasm, and that it cannot be concluded from the fact that agglutinating response has not been obtained from a particular vaccine that increased opsonic, sero-bactericidal and hæmobactericidal power will make default. General considerations show that purely superficial reactions—such as are agglutinating reactions—tend always to be more strictly specific, while reactions which go deeper and affect the central ring of the microbic protoplasm tend to apply within wider limits.

Collateral or Non-Specific Immunising Effects.

There is, in point of fact, ample laboratory proof that every inoculation process has a wider range of action than earlier workers suspected. It would appear that all our ordinary vaccines (so far as these have been tested) not only produce a specific immunising response but also a non-specific effect; and that they render the blood bactericidal to a whole assortment of different microbes. For example, a typhoid vaccine will not only engender antibodies to the typhoid bacillus but will, at any rate for a time, render the blood more powerfully bactericidal to both the staphylococcus and the streptococcus.

With regard to the application of this to prophylaxis, it deserves to be noted that, as is exhibited in the statistical results of anti-pneumonia inoculation applied in African natives in the Premier Mine (*vide* Wright, "Drugs and Vaccines in Pneumonia," Constable, London, 1914), the pneumococcus vaccine employed gave not only good protection against pneumonia but also, as shown by the conspicuous decrease of the "mortality from other causes," considerable protection against other infections.

2. Question as to how the Optimum Doses of Vaccine for Ordinary Prophylactic Inoculation should be arrived at.

The proper procedure for finding the optimum dosage for prophylactic inoculation is to take a series of healthy men, to divide them into groups of at least three or four individuals, to inoculate each group with a different dose of vaccine, and then to test the bloods from day to day so as to plot out the curve of immunising response. The optimum doses will be those that will, after a transient negative phase and strictly moderate local reaction and constitutional disturbance, give the best positive immunological response, *i.e.*, the greatest production of antibacterial substances and the greatest hæmobactericidal power.

3. Should a Prophylactic Procedure consist, as in Anti-Smallpox Vaccination, of a Single Operation, or should two or more Inoculations be Undertaken ?

The practice of proceeding in prophylactic immunisation by successive stages—using for the first inoculation a weaker, and for the second a stronger vaccine—dates back to the Pasteurian anti-anthrax inoculations—the first prophylactic procedure in which regulated vaccines were employed. Here it was definitely shown that the first vaccine which consisted of a fully attenuated living culture conferred protection against the less attenuated living culture called Vaccine No. 2 ; but that the desired protection against virulent germs was obtained only after the double inoculation.

Quite comparable phenomena manifest themselves after prophylactic inoculation with dead cultures. Here, as seen characteristically in connexion with antityphoid inoculation, a first injection generates protective substances which render the patient less sensitive to the typhoid poison. In virtue of this a double dose of the vaccine can be administered in the second inoculation ; and this double dose has the effect of sending up the bactericidal power to a level higher than that attained after the first dose.

The question as to whether progressively increased protection can be obtained by recourse to further inoculations with increasing or non-increasing doses has not yet been adequately investigated. This will certainly depend on the quanta of vaccine employed in the first and second inoculations. For there is a quite definite limit to the organism's power of immunising response. For example, when continuously increasing doses of cultures or toxins are inoculated into horses with a view to the fabrication of antibacterial and antitoxic sera, there is obtained, when certain limits are exceeded, not progressively increasing immunising response, but progressively increasing insensibility. Similarly in long-standing streptococcal septicæmias the human organism acquires a comparative insensibility to streptococcal vaccines. And both in men and animals a similar imperturbability to tuberculin develops in the last stages of tuberculosis.

4. Dosage for Prophylactic Inoculation undertaken in the Presence of Infection.

What has been said above refers to prophylactic inoculation conducted in the absence of infection. A different scheme of dosage should be employed when prophylactic inoculation is undertaken in the presence of an epidemic. The conditions are then, of course, such that the candidate for inoculation may be actually incubating the disease, or may immediately afterwards be brought in contact with the infection. In either circumstance it would (in view of eventual risks attaching to the induction of a negative phase) be prudent to employ for the first inoculation a reduced dose of vaccine. If the patient is uninfected, the proper dose would be that which just fails to produce a negative phase in the healthy. If the patient is already infected, his proper dose would be that same quantum curtailed in accordance with the principle explained in section 4 (see *infra*, page 15.)

II.—Prophylaxis against Influenza and Catarrhal Infections of the Respiratory Tract.

The theoretical and practical problems encountered here are, as a moment's consideration will show, far more complex than any which have to be dealt with in connexion with diseases of simple etiology such as plague, typhoid, Malta fever, cholera and epidemic pneumonia. We have in influenza and certain other catarrhal affections of the respiratory tract to take into account that we may conceivably be dealing with a primary infection by a so-called filter-passing organism complicated with a supervening bacterial infection; further we have to note that the bacterial infection dealt with in these infections is a multiple infection; and, lastly, we must keep in view that many catarrhal respiratory affections are not infections derived from outside but *auto-infections*, i.e., exacerbations of subsisting surface infections of the respiratory mucous membranes.

In this last case the problem to be dealt with is obviously not a simple prophylactic problem; what is required is treatment directed to the extinction of the subsisting surface infection, supplemented by a general fortification of the organism against microbic attacks. This will be dealt with later. Where we are dealing with recurring infections from outside, as distinguished from auto-infections, what would, from the theoretical point of view, seem to be required would be a combination of non-specific with specific immunisation—non-specific immunisation against eventual unknown filter-passing agents, and specific immunisation against all the more important pathogenetic microbes that affect the respiratory system.

It will suffice to point out that despite the many difficulties of this problem—difficulties of choosing the proper combination of microbes, and the best doses of each—prophylactic inoculation against colds has in point of fact been attended by a considerable amount of practical success.

VACCINE THERAPY PROPER.

Factors upon which the Success of Vaccine Therapy Depends.

Introductory.

Vaccine treatment can give a satisfactory percentage of good results only when the following conditions are complied with :

(1) The nature of the bacterial infection must have been ascertained, and the vaccine employed must be derived from a species of microbe which will, when inoculated, furnish the antibodies required for combating the patient's infection.

(2) The general principles of dosage must have been mastered ; the doses which are applicable respectively to lightly and heavily infected cases must be approximately known ; and the law of the negative and positive phase (*i.e.*, the law that large doses of vaccine temporarily reduce the resisting power of the blood while small doses produce immunising response unpreceded by reduced power) must be appreciated.

(3) The doctrine of the ephylactic (or non-bacteriotropic) nidus must be kept constantly in mind. In other words it must be appreciated that except in definitely septicæmic diseases, microbes survive and flourish in the organism only in *niduses*, or as we may more familiarly call them holes and corners, where the leucocytes are held at bay by bacterial toxins, and the antitryptic power of the blood fluids has been locally abolished. These fluids have been depleted also of their bacteriotropic and, in particular, of their bactericidal elements by unloading them upon the microbes which happened first to come in contact with them—either those which arrived earliest in the nidus or, in case of conglomerations of microbes, those most superficially situated.

It follows from the consideration of these conditions that it will always be advisable, and will generally be indispensable to the achievement of therapeutic success, to evacuate abscesses and lesser collections of pus. Where an abscess has been laid open, the corrupted fluids in the encasing walls must be drained off, either by the application of hot fomentations or of 5% salt solution. Until that is done the leucocytes and uncorrupted blood fluids cannot, or can only with difficulty, come into application upon the infecting microbes.

(4) The important rôle played by spontaneous and artificial auto-inoculations must be appreciated. In other words, it must be understood that spontaneous and passive movements and also all other influences which cause the blood or lymph stream to flow more rapidly through a nidus of infection, inevitably bring dissolved bacterial elements into the blood stream, and are thus equivalent to the

inoculations of smaller or larger (and, of course, unmeasured) quanta of vaccine.

(5) Candidates for vaccine treatment must be classified into :

- (a) Those who are uninfected or only lightly infected. These can be treated with full or nearly full doses of vaccine, and here treatment is perfectly simple.
- (b) Those that are heavily infected and are suffering from bacterial auto-inoculations with pyrexia and constitutional disturbance. These must be treated with reduced doses of vaccine (the dosage being always inversely as the severity of the infection), and the successful conduct of the operations is inevitably intricate and difficult.
- (c) Those suffering from overwhelming infection and whose faculty of making immunising response is paralysed. When the infection has gone so far that the patient can no longer make immunising response, vaccine treatment is not only futile but definitely contra-indicated.

Enough has been said in the foregoing to show the thoughtful reader that, in the very nature of things, definite limitations attach to vaccine therapy, and that these, in the nature of things, cannot be removed by inventing new vaccines or special antigens. And also enough will have been said to bring it home that vaccines will always find their principal and most useful field of application in prophylactic inoculations, in the treatment of localised infections, and in the earlier stages of the graver infections.

It will now be necessary to elucidate certain of these points further. We may, as in prophylactic inoculation, begin with the

Question as to how nearly the Microbe which furnishes the Vaccine must be related to the Microbe which is to be Combated.

Two main questions must here come up for consideration. *First*, that already touched upon above (*vide* under Prophylactic Inoculation, pages 4 to 7) as to whether a vaccine can confer protection against a species of microbe different from that which has been employed in its manufacture. *Secondly*, the narrower issue as to the comparative advantages of autogenous and stock vaccines.

With regard to the former, much research work will have to be done before it becomes possible to say definitely what therapeutic effects can and cannot be achieved by vaccines other than those made from the species of microbe from which the patient is suffering.

But recent research has thrown entirely new light upon the general problems here involved. It has been established that, when vaccine is introduced in appropriate doses, directly or indirectly, into the blood *in vivo*, or is added to the blood *in vitro*, or is added to serum and then brought in contact with leucocytes obtained from the shed blood, this immediately effects an increase of the bactericidal action of the blood or blood fluids. Such bactericidal

action is exerted not differentially upon the species of microbe that has furnished the vaccine, but non-differentially upon a variety of other microbes.

These are facts which compel us to assume that bactericidal substances (and, it may be added, also other non-specific anti-bacterial elements) are stored up in the leucocytes, and that these are, as soon as a proper stimulus is applied, extruded into the blood fluids. We may speak of this phenomenon as immediate or *subitaneous* immunising response. It should be noted in connexion with the subitaneous immunising response that it is generally very evanescent—the blood usually reverting to the *status quo ante* in less than 24 hours.

We must clearly distinguish from this subitaneous non-specific immunising response the later specific response. Here, in response to the vaccinating stimulus, newly generated antibacterial substances appear in the blood, and these would appear to be definitely specific, *i.e.*, to act only upon the particular species of microbe which has furnished the vaccine.

We are not as yet in a position to say how much of the effect of therapeutic inoculation is to be ascribed to the subitaneous and non-specific, and how much to the later-developing specific immunising response. One surmises that the immediate clinical effects of inoculation (and these, when carefully looked for, will often be detected) must be attributed to non-specific immunising response; and the later effects to the specific response. But in any case, in whatever proportions the credit should be partitioned out, it would seem obvious that it will be a desideratum to obtain for each patient all that can be obtained from both kinds of immunising response. That will mean that it will be desirable to employ in the ordinary case always the specific vaccine, in other words the vaccine made from the same species of microbe as that from which the patient is suffering.

That point settled, we may now go on to consider the

Comparative Advantages and Disadvantages of Autogenous and Stock Vaccines.

The general advantage possessed by an *autogenous vaccine*—vaccine which has been made from the actually infecting microbe—is that it can be trusted to engender the specific bacteriotropic substances desired. The general disadvantages of such a vaccine lie: *first*, in the fact that the fabrication of autogenous vaccines involves the expenditure of appreciable labour or money; *secondly*, in the fact that autogenous vaccines are in certain classes of cases unprocurable, and that they are in others, where the actually infecting microbes are mixed up with numerous contaminating microbes, only doubtfully authentic; *thirdly*, in the fact that autogenous vaccines (and this, in rapidly progressing infection, is a vital consideration) can never be immediately available; and, *fourthly*, in the fact that when a vaccine is to be used only upon a single patient there cannot, from the nature

of the case, be the same inducement to lavish work upon it, standardise it and test it, as there is when a vaccine is to be employed upon a very large number of patients.

The general advantages of a *stock vaccine* lie in the fact that labour and money are saved; that vaccines are available for cases where autogenous vaccines are unprocurable or only with difficulty procurable; that these vaccines are immediately available; and that it now becomes practicable to devote proper time to the processes of standardising and testing.

The disadvantage which attaches to a stock vaccine is that we have not the same guarantee as in the case of an autogenous vaccine, that the microbes employed in the manufacture will accurately conform to those which require to be combated. To provide against the possibility of failure from this cause stock vaccines are, when the species of microbe concerned tends to run into different strains, manufactured from a number of such strains. Such *polyvalent* homologous vaccines would commonly be described as vaccines which contain, in association with a useless ballast of non-requisite, a useful quantum of the required microbes. But they would perhaps be more accurately described as vaccines which contain, in addition to the strain the patient most requires, also other strains which may by eliciting a non-specific immunising response contribute their quota to the therapeutic effect.

Illustrations of the Points brought out above.

From the point of view of the possibility of treatment with autogenous vaccines cases may be ranged in three classes. There is:

- (a) *The case where the nature of the bacterial infection is known but a culture of the microbe cannot, or can only with great difficulty, be obtained from the patient.*

This is the case which presents itself in non-pulmonary tuberculosis, in gonorrhœal rheumatism, in actinomycosis, in certain cases of acne, and generally where we are dealing with pathogenetic microbes which are few in number, or troublesome to grow, or difficult of access.

- (b) *The case where, owing to the profusion of contaminating microbes it is difficult to identify and isolate in culture the specific infecting agents, and to be sure that we can provide an authentic specific vaccine.*

This is the case that presents itself when we are dealing with pyorrhœa, with bronchitis and catarrhs affecting the respiratory passages, with intestinal infections, with many discharges from the ear and uterus, and also with putrid wound infections and ulceration in malignant disease. In all of these cases the specific infecting microbes from the interior regions of the body and the deeper structures will be intermixed with adventitious microbes: (a) from the more superficial layers, (b) from the outer passages and cavities of the body, and (c) from external sources. And as further complications these saprophytic microbes will proliferate more rapidly in the voided excretions

than the genuinely infecting microbes. And again, they will grow much more freely on the ordinary nutrient media of the bacteriologist. It follows that a so-called autogenous vaccine (unless prepared by an experienced and very conscientious bacteriologist who has at disposal perfectly fresh material and is in a position to make, in all cases of doubt, repeated bacteriological examinations) may furnish only a very unsatisfactory representation of the infecting microbes. The practical conclusion from this is that where we have a choice between an autogenous and a polyvalent stock vaccine it will (unless we can be certain that we have in the autogenous vaccine an accurate and complete representation of the infecting microbes) be advisable to use the stock vaccine. For the inferior kinds of autogenous vaccines will often consist of contaminating saprophytic organisms, while reputable stock vaccines will have been made from microbes that are definitely pathogenetic.

- (c) *The case where a culture of the infecting microbe or microbes can be readily obtained, and can be obtained without any admixture with contaminating microbes.*

This is the case which presents itself, for example, in furunculosis, sycosis, many cases of acne, erysipelas and cystitis.

Here we are quite free to choose between employment of an autogenous and a stock vaccine. A few examples will serve to bring out certain less obvious considerations which should be taken into account in making choice between autogenous and stock vaccines.

Furunculosis and other Staphylococcus Infections.—The points which are here to be regarded are: (a) the fact that the different strains of staphylococcus found in these infections do not vary widely the one from the other, (b) the fact that in furunculosis and similar troubles we have a number of different and probably independent infections, and can never be sure that the strain of staphylococcus which has been obtained from one of a patient's furuncles will be closer kith and kin to that in his other furuncles than would be the strain employed in making the stock vaccine.

Acne.—The points made in connexion with furunculosis apply also here where we have as a rule a mixed acne bacillus and staphylococcus infection. But they apply with a difference, for the acne bacillus is a species which includes a large number of different strains, of which often more than one may be found in one or other acne pustule. It will therefore seem specially expedient to employ in the treatment of acne a stock vaccine in which there are comprised a number of different strains. Moreover, it is not always easy to cultivate the acne bacillus.

Erysipelas and Streptococcal Lymphangitis.—Here, as in the case of ordinary furunculosis, we are practically always dealing with one and the same variety of microbe—the *streptococcus pyogenes*. It may consequently be almost confidently assumed that the microbes which are affecting the patient are closely conformable to those employed

in making the stock vaccine. Further, and this is the most important factor in the treatment of erysipelas, the vaccine should be applied at the earliest possible moment. This of course involves the employment of a stock vaccine.

Coli-Cystitis.—Here we are dealing with a microbe of which there are a large number of very different varieties. That, taken together with the fact that we have here instead of multiple foci of infection only a single focus, and in this a continuous infection, and further that coliform microbes can be rapidly and easily cultured, would seem to plead in favour of using autogenous vaccines in coli-cystitis infections.

DOSAGE IN VACCINE THERAPY.

1. General Principles Involved ; Requirement that the Medical Practitioner shall take upon himself the Responsibility for the Doses.

When it is a question of prophylactic inoculation it is, as we have seen, practicable for the scientific worker who prepares the vaccine to prescribe a fixed scheme of doses. The prescription of one and the same first dose for all candidates for prophylactic inoculation is, as we saw, justified by the circumstance that these candidates are all normal individuals. And in like manner, the prescription of a larger dose of vaccine for use in the second inoculation is authorised by the fact that all those who come up for this inoculation will come up to it with enhanced powers of resistance.

In vaccine therapy all the conditions are different. We are not here working up to a cumulative effect in which a large reserve of antibacterial substances will be circulating in the blood. We here try to provide, in a series of relays and as effectively as possible, antibacterial substances which will, as soon as they become available, be expended in the destruction of infecting microbes. The choice of dosage which will conform to this programme will vary from case to case. Our initial dose will, as explained in the next subsection, vary according as we make choice of this or that special scheme of attack. Again, the dose will vary according as we have to deal with a light or a heavy infection; and yet again it will vary according as we are or are not confronting a microbe which is seriously dangerous. All this will also apply to subsequent inoculations. But it will apply with the difference that in later inoculations the magnitude of the dose will be determined largely by the results following those which have preceded.

It will, by consequence, be absolutely essential for the medical practitioner to take upon his own shoulders the responsibility for the doses which he brings into application. His taking up of that responsibility can, however, be facilitated (*a*) by setting out, as is done in the next following subsections, the different special schemes

of therapeutic attack which lie open to selection ; (b) by explaining in what manner dosage is influenced by the volume of the patient's infection ; and (c) by furnishing certain practical hints as to the procedure to be adopted in the different types of cases.

Furthermore, matters can be made convenient for the practitioner by issuing vaccines in such a series of graduated strengths as will furnish in a convenient bulk all the various doses of vaccine that will be likely to be required.

2. Requirement that the Medical Man shall, before he begins Vaccine Treatment, make up his mind what is to be his immediate Therapeutic Objective.

Where we contemplate using vaccines for the treatment of an infection the question we have to decide with ourselves is the question as to what is to be our immediate clinical objective.

- (a) **We may aim at immediate Improvement in the Patient's Condition, and may be Content to ask from a first Inoculation only very fleeting Improvement, provided that we can Achieve this without in any way Aggravating the Patient's Local or General Condition.**

Cases will often present themselves where even a temporary aggravation of the clinical conditions will be inadmissible. Our deterrent may here be the possible flaring up of the local infection, the possible increase of pain, the possible aggravation of respiratory distress, the possible transformation of a localised into a generalised infection, or any such aggravation of the patient's symptoms as will result in laying him up. Fear of exacerbating the localised infection and aggravating pain should influence us when we are dealing with phlyctenules and corneal ulceration, tubercular ulcers of the bladder or larynx, acute cystitis or an acutely inflamed joint. In asthma the risk of bringing on an attack or aggravating it should occupy our minds. In the treatment of a painfully placed furuncle (such as a furuncle of the external auditory meatus) or of acne, or an incipient stye on the eyelid, or a developing cold, the question of disfiguring the patient or aggravating his pain or temporarily incapacitating him should not be lost sight of. Lastly, in the treatment of erysipelas, acute gonorrhœa, and incipient phthisis, the graver kind of risks—those of a spread of microbes into the blood and a generalisation of the infection—should be constantly present to the mind.

But these considerations should not persuade us to turn away from the employment of vaccines. What they should induce us to do is to employ in these cases only such quanta of vaccine as will not produce any negative phase.

- (b) **We may with a view to Securing for the Patient Greater After-Advantage be Prepared to Ask him to Endure the Temporary Set-back Associated with the Production of a Slight Negative Phase.**

We can in connexion with the treatment of most chronic localised infections quite well afford, with a view to subsequent advantage, to induce slight and transient negative phases. This may, for example,

be done as a routine in connexion with the treatment of acne and furunculosis, chronic infections of the mucous membranes and indolent tubercular infections of the glands and joints or subcutaneous tissues.

- (c) **We may for the Purpose of bringing a Local Focus of Infection into a more Wholesome Condition be Prepared to Induce a more Pronounced Negative Phase.**

This procedure will be justified in the case of indurated tubercular glands, and in the case where a carbuncle is sapping the strength of the patient. Here the administration of a dose of vaccine sufficiently large to induce a marked negative phase will often save the situation by inducing, as the case may be, suppuration in the tubercular glands or, in the case of a carbuncle, rapid shelling out of the necrosed tissues with a restoration of wholesome conditions in the wound.

3. When the immediate Therapeutic Objective has been Chosen, how can the Dose of Vaccine which is appropriate for the Achievement of that Purpose be Discovered?

The most direct way of finding the dose of vaccine required is to take a series of samples of the patient's blood, to add to them a series of different quanta of vaccine, and then to determine what is the smallest and what is the largest quantum of vaccine which when added to a volume of the patient's blood will induce immunising response *in vitro*. Having in this way arrived at the minimum and maximum number of, let us say, staphylococci or streptococci to which 1 c.c. of the patient's blood will make immunising response we then multiply by the number of c.c. of blood contained in the patient's body (obtaining that number by dividing his body-weight in kilos and grammes by 13), and so arrive by arithmetical calculation at a dose which should induce in the patient's blood, *in vivo*, the kind of immunising response which is sought for. In practice a dose somewhat smaller than that given by this calculation will produce the kind of response we require.

When this method of fixing the dose is, owing to external circumstances, inapplicable, it will be necessary to choose the doses by regarding those (specified later) which clinical experience has shown to give in ordinary (*i.e.*, in comparatively lightly infected) cases the particular type of response which we want to obtain.

In such choosing another important therapeutic principle should, however, be regarded.

4. Principle that the Volume of the Patient's Infection must Regulate the Dose—the Dose of Vaccine given being inversely as the Volume of the Patient's Operative Infection.

The dosage for the infected is not the same as for the uninfected. The reason for this is that the infected patient (who cannot be assumed to have an increased faculty of immunising response) will, when he is inoculated, have to deal with two quanta of microbes : (a) the quantum

administered in the vaccine, and (b) the quantum represented by what we have called operative infection, *i.e.*, the number of microbes actually affecting his blood. This quantum must be allowed for by proportionately curtailing the dose of vaccine administered.

The rule for its curtailment must be expressed in symbols. If X stands for the volume of vaccine that would in the uninfected man produce the kind of response we want, and if Y stands for the quantum of infection in our patient, the dose we should give him would be $X - Y$. If for example $Y = \frac{1}{4}X$, the proper dose will be $\frac{3}{4}X$. And if $Y = \frac{1}{2}X$, the proper dose will be $\frac{1}{2}X$, and so on; the dose becoming with every increment of infection smaller and smaller until we arrive at a point when Y—the operative infection—exceeds any dose which could be responded to by the healthy body.

On pursuing this line of thought two important consequences are reached: (1) the efficacy of vaccine therapy will, taken generally, be inversely as the volume of the patient's infection. For the maximum dose that can be usefully applied will become smaller and smaller as the volume of the patient's infection becomes larger and larger; (2) When the patient is so gravely infected that his blood has to deal with a volume of microbes greater than any healthy blood could respond to, vaccine therapy will be contra-indicated or must at any rate be limited to the subcutaneous injection of doses curtailed to such an extent as not to overflow into the blood.

What requires to be said on the treatment of such desperate cases may conveniently be postponed until we have considered the treatment of those which are capable of making response to the inoculation of vaccines. It will be convenient to subdivide these cases into: (a) ordinary localised infections which have little or no tendency to produce severe constitutional symptoms or to develop into general infections, and (b) those which may readily assume a serious form.

- 5. Principle that when in Serial Inoculations a Dose which gives a Satisfactory Therapeutic Result has been arrived at, such Dose shall, so long as the Patient continues to improve, be adhered to. Further, that this Scheme of Dosage shall not be departed from except where the earlier Inoculations have achieved the Extinction of the Infection and the later have, in consequence, a purely Prophylactic Aim.**

In view of the fact that the doctrine which prescribes the employment of geometrically progressive doses in vaccine therapy finds an echo in practically every mind, the reader may here be specially warned (a) that this doctrine originated in the domain of prophylactic inocula-

tion ; (b) that, even here, the doctrine applies only, as we have seen, within a definitely restricted range of doses ; and (c) that this principle of employing always continuously increasing doses has been quite illegitimately imported from its domain of origin into that of vaccine therapy.

Full consideration will show that the doctrine here under discussion comes into conflict with the fundamental principle of vaccine therapy, that we should, in choosing our therapeutic doses, take into regard not only the quantum of antigen we propose to incorporate but also the antigen contributed by the microbes at work in the patient's organism.

That we have here conflicting principles will emerge when it is considered that we cannot, at any rate where we are dealing with a heavy infection, expect that infection to be reduced at such a pace as would, for example, warrant our doubling our vaccinating dose on each successive occasion. And even if it were practicable to rid the organism of infecting microbes at that rapid pace any scheme of geometrically advancing doses would very soon bring into application quanta to which the organism, even though it might not visibly resent them, could never make proper response.

Our natural impulse to bring into application continuously increasing doses having been held in check by these considerations, the alternative principle of adhering, so long as this continues to be operative, to the smallest dose of vaccine which gives good clinical results will obviously recommend itself for adoption.

Programme of Treatment for those Cases of Localised Infections where the Induction of a Negative Phase need not be Sedulously Avoided.

Here it will be advisable to begin with the initial dose indicated under the heading of the particular vaccine. The patient must then be kept under observation to find out whether there has or has not been any change of condition, and if so whether it has taken the form of (a) immediate but very transient amelioration, or (b) a temporary set-back followed by improvement, or (c) an unqualified set-back. To use technical terminology, we have to enquire whether there has been any indication of the induction of an immediate positive phase, or of a negative phase followed by a positive, or of an unrelieved negative phase.

The *negative phase* will manifest itself, where it is a question of a cutaneous infection, in a visible exacerbation of the local disorder. In glandular infections it will show itself in increased swelling with tenderness, or threatenings of suppuration. In arthritis the joints will become tenser and more painful. In cystitis there will be increased urgency and frequency of micturition.

When, by reason of the site and character of the infection, local indications make default, it will be necessary to judge by the constitutional effects. The negative phase will express itself not only in pyrexia but also in malaise and indisposition. In children it will very plainly manifest itself in moping and tetchiness.

The occurrence of a *positive phase* will manifest itself in local improvement and in a characteristic feeling of well-being; children who have been depressed and ailing become lively and cheerful.

If there are no symptoms of either a negative or a positive phase, or if there has been only very transient improvement followed by a rapid return to the *status quo ante*, the dose of vaccine may appropriately be increased.

If inoculation has caused a definite set-back the patient must be allowed to recover fully before the next dose is inoculated, and then, as an ordinary rule, the dose should be reduced. But judgment must here be exercised, and if more than an equivalent of benefit has, after the passing away of the negative phase, been achieved, the dose may be adhered to. Where, even after gradual advance to the maximum doses set down for the particular vaccine, neither negative nor positive phases come under observation, it is doubtful whether advantage will be obtained from continuing the inoculations. But occasionally in such refractory cases benefit may be obtained from resort to still larger doses. But in all such cases—and they fortunately are exceptional—the lack of all clinical guidance makes the treatment very unsatisfactory.

In the ordinary chronic localised infection the inoculations may conveniently be given once a week or once every ten days.

Programme of Treatment for those Cases of Localised Infection where the Induction of a Negative Phase might entail Grave Consequences either in the form of Aggravated Pain or Extension of the Infection in Important Organs, or in the form of Pyrexia with the Production of Metastatic Foci or a Generalised Infection.

Here—and the forms of infections here specially in view are streptococcal lymphangitis and erysipelas, acute gonorrhœa, tuberculous ulceration of the bladder and larynx, and pulmonary phthisis—vaccine therapy must always be conducted with a maximum of precaution; and it is fundamentally important to avoid the induction of any negative phase.

The appropriate initial dose will be the smallest quantum of vaccine which is effective. And—since the effect of such minimal doses will be very transient—it will, in acute cases in which the patient is holding

his own, be a proper procedure to reinoculate at intervals of 24 or even 12 hours, slowly increasing the doses and lengthening out the intervals as the volume of the infection diminishes.

Treatment of Early Cases of Fulminating Infection—Cases where it is Dubious whether the Patient is still in a Condition to make Immunising Response to Vaccines.

The question as to whether a patient who is the subject of a very acute, rapidly spreading infection will or will not be able to respond to the inoculation of a vaccine can be answered : (a) by testing the phagocytic efficiency of his leucocytes ; and (b) by undertaking a vaccine response test—i.e., by making graduated additions of vaccine to samples of his blood *in vitro* and seeing whether here any immunising response is obtained, and if so with what dose of vaccine it is obtained (*vide* Wright, Colebrook and Storer, "New Principles in Therapeutic Inoculation," *Lancet*, February 24th, March 3rd and 10th, 1923).

When these laboratory tests cannot be carried out, it will be proper to give the patient the benefit of the doubt ; to take chances, and administer without delay a minimal effective dose of the vaccine. For there will, if the blood is not yet seriously infected, still be fair prospect of success.

Treatment of Definitely Septicæmic Cases and Cases of Long-Continued Hectic Pyrexia.

Here it will be necessary to resort to *passive immunisation*—in other words, to supply from without the antibacterial substances which the patient stands in need of.

This means resort to either *serum therapy* or *immuno-transfusion*. The difficulties in the way of successful serum therapy lie in the obtaining of antibacterial sera which shall be of sufficient strength and also compatible with the patient's blood.

What serum therapy tries under difficulties to effect can with greater security and success be obtained by *immuno-transfusion* : i.e., by the transfusion of compatible human blood obtained from a donor who has made active response to a vaccine (Wright, *Lancet*, 1919, I., 489 ; Wright, Colebrook and Storer, *Lancet*, 1923, I., 473). The scientific basis of this method is furnished by the following facts : (a) Immunising response to a vaccine can be obtained within a period of a few hours after hypodermic inoculation, and more rapidly after intravenous injection ; (b) The increased bactericidal power engendered comes into effect not only upon the species of microbe which has furnished the vaccine but also upon other species. For example, increased killing of streptococcus can be obtained indifferently by an inoculation of streptococcus or staphylococcus vaccine ; and

increased killing of staphylococcus indifferently by staphylococcus or streptococcus vaccine (*vide* Wright, Colebrook and Storer, *loc. cit.*).

The successive steps in immuno-transfusion are as follows : (1) the choice of a donor whose blood is compatible with that of the patient ; (2) his preparation by the intravenous or subcutaneous inoculation of a suitable dose of vaccine ; (3) the drawing off and defibrination of his blood ; and (4) the transfusion of this immunised defibrinated blood into the patient. (For details of the procedure and a record of the results obtained, see Colebrook and Storer on Immuno-transfusion, *Lancet*, 1923, ii., 1,341.)

After-Treatment for the Prevention of Relapses and Reinfections from Without.

Where an infection has been reduced to insignificant proportions or has been extinguished by vaccine therapy, the question immediately arises as to whether it will not be possible to embark on prophylactic procedures for the prevention of fresh attacks.

A distinction must here be made. Where it has been a question of an invasion of the deeper tissues (as distinguished from infections of mucous membranes and the epidermis), and in particular where it has been a question of a streptococcic or tubercular infection, the point of essential importance is to secure the complete extinction of the focus of infection, for such a focus, if left alight, may flare up again into an infection. The inoculations should, with a view to the prevention of this, be continued till long after all clinical symptoms have disappeared. When once this infection has been finally extinguished it would appear to be unnecessary to resort to any periodical prophylactic procedures. The same holds true of staphylococcic inoculations. These should be continued until every trace of induration has vanished. But when that has been achieved, and the skin is everywhere in a condition to put up a good defence against invasion from without, the inoculations may safely be discontinued. It will be remembered in this connexion that staphylococcus infections, should they recur, can practically always be nipped in the bud by an inoculation of a small dose of vaccine.

In catarrhal infections of the mucous membranes, and in acne, a quite different problem has to be faced. Here, owing to the fact that the external surfaces of the mucous membranes and the sebum in the sac of the sebaceous glands are ephyllactic regions—*i.e.*, regions which cannot be watched and guarded against bacterial infection by the blood—we cannot hope to achieve complete extinction of the infecting microbes. In consequence of this it will be futile in these cases to prolong the inoculations with an idea of extirpating the infection, and the best policy will be to give periodical inoculations with a view of keeping the microbes at bay.

KEEPING PROPERTIES OF VACCINES.

The question as to whether vaccines lose some of their efficacy by keeping or maintain their properties intact is one which owing to experimental difficulties cannot be answered in terms of a definite yes or no. It is true that it is a comparatively simple procedure (a) to take a dose of new vaccine which contains a counted number of microbes, and a similar dose of an old vaccine which contained when originally counted an equal number, and (b) to inoculate these doses into a couple of men or animals, and then (c) to follow this up either by measuring the antibodies produced, or, by directly ascertaining, if the animals employed are by nature susceptible to the species of microbe in question, whether the vaccines have conferred immunity. At the same time, such simple experiments, though they show quite conclusively that successful immunisation can be obtained with vaccines which are very many years old, cannot decide the question as to whether vaccines do or do not, with the progress of time, lose some portion of their immunising property.

To settle that point, instead of operating with only a single dose of each vaccine, and only a couple of men or animals, it would be necessary to employ a graduated series of doses of both an old and a new vaccine, and further, since individual men and animals differ in their power of immunising response, to inoculate each dose into a group of individuals instead of into a single man or animal. And finally, if after such complicated experimentation, it became clear that the weaker doses of the older vaccine gave the same or, as the case might be, less immunisation than the doses of the fresh vaccine, it would then have to be borne in mind that this result had application only to the ageing of one particular sample of vaccine—a sample which might have been kept in specially favourable or specially unfavourable conditions. From that it becomes plain that for the obtaining of information which would have a general application it would be requisite to duplicate and reduplicate such extended tests. And clearly an essential preliminary to that would be to obtain much simpler methods of procedure.

In connexion with this all that can be said for the moment is that it is hoped that it may prove possible to substitute for the testing of each individual dose of both an old and a new vaccine upon a group of animals or men *in vivo*, a trustworthy *in vitro* method for testing all the doses of both vaccines upon samples of one and the same blood. Pending the achievement of some such procedure we must perforce content ourselves with information drawn from methods of indirect inference.

Consideration will show that inferential evidence as to the keeping properties of vaccines can be derived from all the various methods of examination which are set out below.

(1) Microscopic examination of unstained and appropriately stained preparations made from old vaccines, can tell us whether the microbes in the vaccines are, or are not, intact, and whether they have, or have not, retained their characteristic staining properties. And a super-added enumeration of the microbes in such old vaccines will, of course, furnish more exact information on the question of the dissolution of the microbes.

(2) Agglutination and phagocytic tests undertaken with the formed elements derived from vaccines of ancient date will give us information as to whether the antigenic elements have or have not been retained in the bacterial bodies.

(3) Inoculations of filtrates and supernatant fluid from vaccines into blood *in vitro*, and into men or animals—followed by measurements of the antibodies produced—will tell us whether antigens have passed out from the bacterial bodies into the suspending fluid.

(4) The measurement of the toxicity of vaccines by biological tests will notify us of any changes that may have occurred in the vaccines. Clearly if the toxicity of the vaccine has not varied it would follow that the vaccine had not altered; and if the toxicity was found diminished this would show that disintegration had taken place. The biological tests which are here applicable are, on the one hand the addition of graduated doses of vaccines to blood followed up by the observation of the influence exerted upon leucocytic emigration; and, on the other hand, in the case where we are dealing with pollen and similar antigens the application of graduated dilutions of these substances to the cutis of those who are sensitive to their action.

(5) Lastly, the examination of vaccines for ferments is capable of furnishing information which will have a bearing on the question as to whether vaccines are likely to undergo disintegrative as distinguished from purely dissolutional changes on keeping. It is immediately obvious that disintegrative changes, if such occurred, might be produced by external agencies such as light and heat operating in conjunction with water and perhaps oxygen. And it is obvious that disintegrative changes might be produced also by ferments originally present in the bacterial cultures, if such ferments, by

reason of their superior stability, survived the sterilising operation to which the microbes had been subjected. The ordinary familiar ferments can be tested for by digesting very concentrated vaccines with the substrata which the living cultures would have affected. For the autolytic ferments which come here specially into regard, the appropriate re-agent and indicator would, as reflection will show, be not the killed and heat—or chemically—fixed microbes which are provided in the vaccines, but the microbes which are furnished by a growing culture.

It will suffice to sum up in a few words, first for those who approach the matter as a problem of science, and then for the practitioner of medicine, the general outcome of the investigations which have been conducted along these different lines.

There is in vaccines on the whole very little dissolution of microbes in, and also very little passing out of antigenic constituents from these into, the suspending fluid. The microbes in practically all vaccines appear to retain for years their form and their characteristic staining reactions. Further, as is shown by the fact that vaccines furnish excellent material for agglutination and opsonic tests, the contained microbes retain their characteristic chemical constituents unaltered. On the other hand, the fact that the supernatant fluids and filtrates of vaccines will produce immunising response both *in vivo* and *in vitro*, and that extreme dilutions will do so *in vitro* shows that some portion of the antigen does pass into solution. Again, measurements of toxicity made by adding old and new vaccines to the blood in graduated doses and determining the influence exerted on leucocytic emigration brings out the fact that there is very little deterioration of vaccines on keeping. Of the bacterial vaccines tested by this method only a few ancient specimens of antityphoid vaccine showed any appreciable diminution of toxicity. Again, measurements of toxicity undertaken with graduated dilutions of a pollen vaccine which dated back 14 years showed that this had during all that lapse of time undergone very little diminution of its power of producing reactions on the cutis of pollen-sensitive patients.

Finally, examination for sugar-splitting, proteolytic, and autolytic ferments has even in the case of the most concentrated vaccines given uniformly negative results.

All the above may be summed up for the practical physician in the statement that vaccines have been shown to be very stable products, and, except in the case of certain specimens of antityphoid vaccine, no indications of deterioration through keeping have been obtained.

GENERAL CONSIDERATIONS.

It may be explained in connexion with the dilutions in which the vaccine is sent out that these are so chosen as to be most generally useful for the treatment of adults, and also to give to the practitioner, without the trouble of dilution, a very wide range of dosage—a range between the dose of vaccine contained in 1 c.c. or more of the most concentrated vaccine and 0.1 c.c. of the weakest dilution.

Only in exceptional cases, and for use upon small children and infants, will the medical attendant require to make any greater dilution of the vaccine.

A further consideration that has been kept in view in issuing the more concentrated vaccines is the convenience of being able, in connexion with the treatment of cases of mixed infection, to combine two vaccines without unduly increasing the bulk of the injection.

It should be carefully noted that the different dilutions of the various vaccines are not to be regarded as graduated doses for routine use in all cases, but to enable the physician to obtain, with facility, minimum, medium and maximum doses, as indicated, in volume suitable for injection.

Choice of a Syringe.

A sterilizable hypodermic syringe is required, the most suitable being either a 20 minim or a 1 c.c. syringe graduated in 10ths or 20ths.

Sterilization of the syringe may be effected by boiling. Where, however, the construction of the syringe allows of the employment of a higher temperature, it may be more rapidly and more effectively sterilized with oil which has been raised to a temperature of 140°C.

The following technique is applicable without special appliances:—

Partly fill a tablespoon with any vegetable oil. Introduce into the oil a bread crumb about the size of half a split pea. Then heat the oil over a spirit lamp until bubbles of steam begin to come off from the bread crumb. The temperature of the oil is now about that of boiling water. Wait till the bubbles have finished coming from the bread crumb—taking an opportunity meanwhile to draw up the oil once or twice into the syringe—and then very cautiously heat the oil up to the point at which the bread crumb shows the first sign of turning brown (about 140° C.). Without allowing the oil to cool down, draw it up two or three times into the syringe, taking care that it comes into contact with every part of the interior.

Drawing off the Vaccine from the Ampoules.

Taking the ampoule which contains the vaccine, first shake up the contents very carefully, then, having sterilized the tip in the flame, break off the point with a pair of sterilized forceps or, in default of forceps, with the sterilized barrel of a small key. The ampoule is now to be inverted over the needle of the syringe held with its point vertically upwards. As the vaccine is drawn off, the point of the needle is to be gradually lowered so as to keep its orifice constantly below the surface of the fluid.

If it is required to withdraw a dose of less than 1 c.c. from an ampoule, the remainder may be preserved for future use if the broken stem of the ampoule is sealed with wax.

Drawing off the Vaccine from the Bottles.

The rubber cap is wired on to the bottle and it is not to be removed. To draw off the vaccine proceed as follows :—Shake up the contents of the bottle. Then place a drop of undiluted lysol on the rubber cap, and, keeping the bottle inverted, puncture the rubber with the needle of the sterilized syringe and draw out the piston till the required quantity of vaccine is taken up.

It will be found that the puncture in the rubber will close up airtight as soon as the needle is withdrawn, and the lysol, if left on the cap will give further security against the entrance of microbes. If, however, the vaccine is not to be in frequent use, before putting the bottle away in a dark place, wipe off the lysol, and, by rubbing over the surface of the cap with a piece of heated glass or metal, melt the wax with which the cap is coated, till it forms an unbroken layer. The negative pressure in the interior may be neglected until, when the larger part of the contents of the bottle has been withdrawn, it is found that the rubber cap is drawn in. It will then be well to equalize the pressure by injecting a few syringefuls of air.

Injecting the Vaccine.

Having filled the syringe, and having measured off on the piston the amount corresponding to the dose it is proposed to inject, pick up a fold of skin and subcutaneous tissue on the patient's flank, thigh, shoulder, chest or back ; with a pledget of cotton wool dab a little undiluted lysol on the skin at the point at which the needle is to be inserted ; and then carry the needle well down into the middle of the fold. After the needle has been withdrawn, carefully remove every trace of lysol from the skin.

The Misuse of Graduated Doses.

It is necessary to emphasize the caution that the various dilutions in which many vaccines are supplied are not intended for routine use in all cases in which vaccine treatment is indicated. Graduated doses are desirable in prophylaxis ; indeed, essential for the production, without undue reactions, of immunity, but doses in treatment should be inversely as the volume of the patient's operative infection, and when the optimum dose has been reached it ought not to be exceeded without very careful consideration. There is reason to believe that much harm may be done by giving massive doses of vaccine in therapeutic treatment, and it is probable that such doses as are sometimes advocated are free from positive danger only because of the harmlessness of vaccines prepared by unscientific methods.

NOTES ON THE USE OF VACCINES.

ACNE VULGARIS.

Acne vulgaris is a disease which is very common but which yet is very difficult to treat successfully. Bacteriologically, it consists of an infection of the sebaceous glands with a bacillus which was described by Unna, and whose cultural characteristics were first (imperfectly) outlined by Sabouraud. This bacillus was called by Unna the Acne Bacillus and by Sabouraud the microbacillus of seborrhœa. The latter name was applied because Sabouraud found that it was also associated with various seborrhœic lesions. The bacillus is essentially an anaerobic bacillus, although it can very easily be acclimatised to aerobic conditions. Indeed, it was originally isolated by Sabouraud, and later by Gilchrist and Fleming, by aerobic methods.

If films are made of the sebaceous plugs or of the comedones which form the minor lesions of acne vulgaris, it will be found that there is to be seen a multitude of acne bacilli—small Gram-positive bacilli which have a more or less diphtheroid arrangement. There may be in those lesions, although there is no sign of suppuration, a fair number of staphylococci, mostly of the staphylococcus albus or, more especially, of the staphylococcus epidermidis albus type. If pus from the acne pustules be examined, the bacteriology is not very different from that of the comedo. There may be staphylococci present, but in a fair proportion of cases of suppurative acne the only organism present in cultures made from the pustules is the acne bacillus. In the more or less acute pustules, however, it is the rule to find staphylococci, and in these cases they may be of the more pathogenic "aureus" variety.

Provision is made for the treatment of the various types of acne vulgaris by the issue of acne vaccines of different concentrations and composition. For the milder cases, where there is little inflammation, a simple vaccine of the acne bacillus may be used, while for the more severe cases where there is a likelihood that there is a secondary infection of staphylococcus two mixed vaccines are issued, one containing a relatively small proportion of the acne bacillus and the other a much larger proportion.

Experience has shown that the most ready response to the vaccine treatment will be evinced by those cases in which there are comparatively few comedones but in which there are many superficial pustules, whereas those presenting only comedones, or those, on the other hand, with large deep-seated and indurated lesions, will prove more resistant and may require inoculations weekly or fortnightly over a period of six to twelve months.

It must be remembered that acne pustules are in reality closed abscess cavities, and just as in other closed abscess cavities it is necessary, in order that the vaccine should have a fair chance, to evacuate the

pus. The provision of drainage, which is so important in dealing with deeper pus collections, is not usually a practical proposition in acne conditions, but its place may be taken by repeated and systematic evacuation of pustules and comedones, which should be persevered with during the course of vaccine treatment.

In a report of some illustrative cases treated at St. Mary's Hospital (*Lancet*, April 10, 1909), Fleming concludes that "in some cases an autogenous vaccine of acne bacillus is necessary, yet experience has shown that in the vast majority of cases great improvement has been induced by the inoculation of a stock vaccine, combined with staphylococcus if an examination of pus has revealed that that organism is present."

Galbraith, also, reviewing his experience of over 100 cases (*Practitioner*, 1912, vol. ii.), expresses the opinion that "vaccine treatment is a striking advance on the older methods of treatment."

Since the same microbes, and in particular the acne bacillus, are usually to be found also in the sebum of cases presenting the greasy scalp of seborrhœa oleosa, and in the hair stumps when alopecia results from this condition, the Mixed Acne Vaccine may also be brought into appropriate application for the treatment of those conditions.

Galbraith (*vide supra*) and Dr. Agnes Savill (*Practitioner*, 1912, vol. ii) have reported several cases so treated with encouraging results.

ACNE BACILLUS VACCINE.

This vaccine is issued for the treatment of those cases in which there is reason to believe that there is a pure infection of the acne bacillus—that is, those cases in which there are comedones and merely superficial pustules without much inflammatory reaction.

Hayden has shown that the acne bacillus can be divided into several groups differing somewhat from each other in their cultural and serological characters. In the acne vaccines now issued these groups are represented (as well as in the mixed acne and staphylococcus vaccines), so that these should have a wider range of efficacy than those originally prepared.

The vaccine is issued in dilutions containing, respectively, 20 and 500 millions of bacilli *per c.c.*

Dosage.—It has been found as a result of long experience with vaccines of the acne bacillus that in some cases very little benefit follows the administration of doses of 5 to 20 millions, whereas if the dose is increased to from 100 to 500 millions an immediate beneficial result is observed. It is not every case, however, that is best suited by these larger doses, and it is wise to commence the treatment with doses of from 5 to 20 millions and only to proceed to the larger doses if the condition does not show signs of yielding to treatment. Doses may be given every 7 to 10 days.

MIXED VACCINES FOR ACNE.

In order to enable the practitioner conveniently to administer simultaneously vaccines of staphylococci and of acne bacilli, mixed vaccines of two different formulæ are supplied.

In the one formula—that of **MIXED ACNE VACCINE "A"**—1,000 millions of staphylococci are combined with 20 millions of acne bacilli in 1 c.c., and this preparation will be found most suitable for the treatment of infections in which it is desired to administer only small doses of the acne bacillus. (*See dosage of acne bacillus above.*)

Where, however, large doses of acne bacillus are to be given, **MIXED ACNE VACCINE "B"**, containing 1,000 millions of staphylococci and 500 millions of acne bacilli *per c.c.* should be chosen.

Dosage.—A suitable initial dose of either of these vaccines when employed as suggested above, is 0.25 c.c.; subsequently, an increase to 0.5 c.c., or even more, may be made with advantage.

STAPHYLOCOCCUS INFECTIONS.

The staphylococcus is a pyogenic organism whose natural habitat is the skin. Although it is present on the skin of normal healthy people, it does not cause any trouble until some condition arises whereby its access to the deeper layers is permitted and the normal resistance is broken down. The degree to which the body is resistant to staphylococcus infections has to some extent been demonstrated by Wright, who has shown that if this organism is planted into blood in reasonable numbers, say less than 4000 *per c.c.*, some 95 to 98 per cent. of the cocci are destroyed. However, staphylococcus infections are very common, and it can only be assumed that something has occurred to impair the normal resistance and permit them to obtain a foothold. The function of the vaccine therefore is to restore the equilibrium between the body resistance and the cocci or make the pendulum swing over in favour of the former.

The staphylococci have been grouped according to the colour of the colonies in the ordinary culture medium. Thus we have the staphylococcus aureus, which gives a golden colony, staphylococcus citreus giving a lemon yellow colony, and staphylococcus albus showing a white colony, in addition to which we have the staphylococcus epidermidis albus, of much less virulence, which rarely penetrates deep into the tissues and is, as a rule, only associated with superficial lesions. It has been shown by Hine and others that when staphylococci were grouped serologically most of the types of staphylococcus pyogenes, aureus, citreus and albus, isolated from human pathological material fall into one group, showing that there is no essential difference between the pathogenic types, whether the colonies be golden, yellow, or white.

Experience has also shown that the immunising response to infection or inoculation by one of these three "types" of cocci is in no sense

a specific response to that one type, but that, in general, a more uniformly good response is obtained from a vaccine made from cultures of the yellow types than from one made from the white varieties.

STAPHYLOCOCCUS VACCINE.

This vaccine is prepared from cultures of staphylococcus obtained from cases of furunculosis, carbuncle, osteomyelitis, acne, etc.

The manifold and diverse morbid conditions in which this microbe plays a chief or a contributory part afford a wide sphere for the useful application of Staphylococcus Vaccine. In this sphere we may recognise many infections of :—

- (a) The subcutaneous tissue—*boils, carbuncles, cellulitis, and styas in the eye.*
- (b) Hair follicles of the beard—*sycosis.*
- (c) Deep-lying structures—*whitlow and osteomyelitis.*
- (d) Sinuses and fistulas.
- (e) Moist, macerated or denuded skin surfaces—*burns, pruritus ani, reddening and pustular affection of anterior nares, eczema, small-pox vaccinations, ophthalmia tarsi, dandruff and irritation of the scalp.*
- (f) Some infections of the nasal mucosa and middle ear.

In conditions which have resulted in a break of the continuity of the cutaneous structures, staphylococci are usually to be found whatever the primary infection may have been, and sometimes, as in impetigo, the staphylococci occur in such profusion as to obscure the primary infection unless this is very carefully looked for.

In some cases the apparent failure of staphylococcus vaccine has been due to the vaccine being used alone, whereas it should have been combined with streptococcus vaccine—the streptococcus being the primary infective agent and the staphylococcus merely a secondary invader. In all cases, therefore, where the nature of a cutaneous infection is not clear, and where a bacteriological diagnosis cannot be established, it is wiser to use the 'antiseptis vaccine' (see page 36) than the staphylococcus vaccine alone.

Staphylococcus vaccine may also be used (alone or in combination with streptococcus vaccine) as a prophylactic measure against the septic infections which may follow upon surgical operations and all wounds, in particular extensive wounds such as burns, or those associated with compound fractures. (See also Antiseptis Vaccine.)

For the practitioner's further guidance the following practical points may be noted :—

(1) The treatment of recurrent furunculosis may be conducted on two somewhat different plans, both of which have yielded very satisfactory results.

By the one plan two or three doses of vaccine are given at intervals of 4 to 7 days until the boil(s) for which the patient first came under treatment, as well as any minor staphylococcal infections, are satisfactorily cured, and the patient is then directed to return at the earliest indication of a fresh boil, in order that this may be aborted by a small inoculation. A few days after this small dose a larger one should be given, to further augment the resistance to staphylococcus, and the treatment then discontinued on the same understanding as before.

By the other plan of treatment, inoculations are continued at intervals of 10 to 21 days for a period of two or three months after the cure of the boil(s) for which the patient was first treated, to the end that their recurrence may be prevented for a much longer period.

(2) In connexion with carbuncle and mature boils, it is often desirable that a medium dose (and by this is meant one of the *larger* medium doses, 750 or 1,000 millions) should be used at the outset, with a view to promoting the rapid breaking-down and evacuation of the semi-necrotic tissues.

(3) Although the inoculation of a small dose of vaccine will sometimes serve to abort an incipient boil or carbuncle, it should not be supposed that this line of treatment for a lesion already matured detracts from the advantage which is secured by a simple incision. Vaccine therapy and surgical drainage for such conditions are complementary procedures, and may be expected to yield the best results in the shortest time.

(4) At the site of inoculation, medium doses of the vaccine will frequently engender a transient inflammatory tenderness, and occasionally such a sharp reaction, with diffuse swelling and cedema, as to suggest the incidence of a septic cellulitis. This condition, should it arise, need occasion no anxiety, and may be confidently expected to subside as rapidly as it arose, within 48 hours of the inoculation. Subsequent inoculations of the same dose will not usually determine so marked a local reaction.

In order to minimise the discomfort of such reactions, the inoculation should be made into a part where the subcutaneous tissues are relatively lax.

Constitutional disturbances are very seldom evoked by staphylococcus vaccine.

This vaccine is issued in three different dilutions, containing, respectively, 100, 500 and 1,000 millions of staphylococci *per c.c.*

Dosage.—Minimum effective dose, 50 to 100 millions; medium doses, 250 millions at the outset, increasing to 750 or 1,000 millions.

STREPTOCOCCUS INFECTIONS.

The streptococcal group of organisms is responsible for a great variety of infections, and it is probable that more disease is caused by members of this group than by all the other bacteria combined. Some of these conditions are of the most acute or fulminating kind, such as puerperal septicæmia or septicæmia following a septic wound ; while others are comparatively mild and without constitutional disturbance, such as impetigo contagiosa, paronychia, or many cases of pyorrhœa alveolaris. It is certainly true that very many individuals go through a large portion of their lives suffering from a streptococcal infection of, say, their gums, without suffering more than a trifling discomfort which does not induce them to seek medical advice, while others with a similar infection may suffer severely and be gravely ill. This difference between individuals is doubtless due in the one case to a very perfect compensation or resistance to infection, while in the other case the compensation has for some reason broken down and a grave poisoning resulted. It was established by Gordon that streptococci gain access to the mouth of a babe within half an hour of its birth, and from that time till death the mouth is never free from these organisms. The intestine soon becomes infected and streptococci are to be found in the intestine throughout life, sometimes in small numbers and sometimes in such large quantities that in culture plates they almost swamp the much more vigorously growing *Bacillus coli* (see Intestinal Infections, page 62).

The classification of the streptococci is as yet unsatisfactory, but it can be made roughly by the action on blood. Thus we have the differentiation into streptococcus hæmolyticus, cocci which in their growth dissolve the red blood cells ; streptococcus viridans which changes the blood pigment, hæmoglobin, into hæmatin and methæmoglobin, this changing the red colour of the blood to a green or greenish yellow ; and thirdly an indifferent group which has no action on the blood pigment. They can also be grouped roughly according to their pathogenic action or the region of the body in which they commonly elect to flourish. Thus we have the streptococcus pyogenes, which as its name implies is a pyogenic organism, *i.e.*, its presence in an infection is accompanied by a marked migration of leucocytes to the infected part with the formation of a collection of pus or a purulent exudate. There are also the streptococcus salivarius type, which is commonly found in the mouth, and the streptococcus fæcalis which is a normal inhabitant of the intestine. In addition to these well-defined types, however, there are numbers of streptococci which differ from each other both culturally and serologically. Some of these may be of the hæmolytic variety and somewhat akin to streptococcus pyogenes, others may be allied to the salivarius type and others to the fæcalis type.

As a general rule it is found that the hæmolytic streptococci, that is, those which are capable of producing a substance which has the property

of dissolving red blood corpuscles, are responsible for the most acute streptococcal infections. Thus we have the streptococcus pyogenes which is responsible for most of the cases of septicæmia (except endocarditis), all cases of erysipelas, most of the cases of acute cellulitis and, as was found in the late war, practically all the acute infections of wounds (apart from gas gangrene). Then there are the hæmolytic streptococci which are found in the throat and in respiratory infections. These in the main differ from the streptococcus pyogenes both culturally and serologically. Great attention was paid to these hæmolytic streptococci by American observers during the influenza epidemic of 1916, as a large proportion of the deaths in the United States from bronchopneumonia following influenza was apparently due to a secondary infection with this organism. Avery and his co-workers showed by agglutination and protection tests that the hæmolytic streptococci which infect the lungs in these conditions could be divided into four distinct groups, so that a stock vaccine aimed at countering these infections, whether prophylactically or curatively, ought to contain representatives of each of these groups. Gordon has shown also that the streptococcus which appears in the inflamed throat in cases of scarlet fever is quite different serologically from the streptococcus pyogenes which is responsible for the clinical conditions briefly outlined above.

The streptococci inhabiting the mouth in pathological conditions are very badly defined and, until better methods of classifying these organisms have been discovered, they can be little better classified than by their action on the blood pigment into hæmolytic, viridans, and indifferent.

For vaccine purposes the mouth streptococci have been grouped conveniently under the name "parodontal" streptococci, a name which means nothing more than a collection of streptococci of different characters which have been found to be the causative organisms in a very varied series of infections of the mouth and, especially, of the gums.

Incidentally, it may here be mentioned that Clarke has shown that in teeth in the earliest stages of dental caries there is to be found a variety of streptococcus, which he has called the "*Streptococcus mutans*," which is capable of producing in a culture medium sufficient acid to destroy the enamel, and which *in vitro* he has shown to be capable of causing a condition of teeth indistinguishable from the ordinary dental caries. Cultures of this organism are now incorporated in the "Parodontal Vaccine" which is sent out.

The streptococci of the fæces probably present the greatest problem in the whole streptococcal field. Normally there are to be found in the fæces some streptococci of the type of streptococcus fæcalis along with a few representatives of other types more or less closely allied to this. In various forms of disease, however, the fæces may show, instead of the normal culture of many *B. coli* and very few streptococci,

an almost pure streptococcal flora, and in most cases this is associated with disease of some kind. In many cases of this kind there is little which troubles the patient but constipation and its attendant symptoms, or it may be that the symptoms are merely abnormal irritability accompanied by, or followed by, very marked nervous depression; in others there may be rheumatoid arthritis, and in others asthma. The connexion between the great increase of the streptococcal flora of the intestine and these diseases is not always a very easy thing to establish, but the very great improvement which frequently takes place in the clinical condition when a vaccine made of these streptococci is administered, makes it very likely that the feeling of lassitude or depression, the arthritis or the asthma, is actually the result of some poisoning from the intestinal streptococci. In asthma again, there can frequently be established by means of the cutaneous test that there is a definite hypersensitiveness to these streptococci.

The varieties of streptococci which may be found in the intestinal contents are very numerous. Sometimes there may be a vast overgrowth of the ordinary streptococcus *faecalis*, but more usually these are relatively scanty while there are vast numbers of the more tender streptococci, mainly of those which fall into the "viridans" group and which more resemble the streptococci of the mouth than the intestinal types. There may also be large numbers of cocci which do not alter the blood pigment at all, and which also resemble streptococci which have the mouth for their normal habitat. Hæmolytic streptococci are not commonly found in the intestine, but they are sometimes to be found in very varied conditions, and it has been shown that in scarlet fever, where many of the lesions are associated with the presence of a hæmolytic streptococcus, there are hæmolytic streptococci present in the intestine in a large percentage of cases.

Hæmolytic streptococci have also been found to be very commonly the infective agent in cases of acute and chronic bronchitis, in broncho-pneumonia and in the broncho-pneumonia which supervenes in cases of influenza. They may also be found associated with other organisms in almost any respiratory infection. As the infection is so often in these cases a mixed one, it has not been thought necessary to send out a simple vaccine of these streptococci, but the various types are incorporated in the mixed vaccines which are issued for the prophylaxis and treatment of respiratory infections, namely, the Mixed Anti-Influenza Vaccine, Mixed Vaccine for Colds and other Respiratory Catarrhs, and the Anti-Catarrh Vaccine.

For purposes of administration of stock vaccines the streptococci may be divided into four groups:—

- Streptococcus pyogenes ;
- Hæmolytic streptococci from the respiratory tract ;
- "Parodontal" streptococci ;
- "Intestinal" streptococci ;
- "Rheumatic" streptococci.

STREPTOCOCCUS PYOGENES VACCINE (Polyvalent).

This is made from cultures isolated from cases of acute or fulminating septicæmic conditions, from erysipelas, cellulitis, septic wounds and other sources. The streptococcus pyogenes is a very definite entity having definite cultural characteristics, and it was shown by Douglas, Fleming and Colebrook that serologically all the strains of this organism are identical, an observation which has subsequently been confirmed by Gordon. It follows from this that in cases where the infection is one of streptococcus pyogenes a stock vaccine will give as good results as an autogenous one, and this is borne out by the clinical results of the administration of vaccine. This is in practice a very valuable observation, as many of these streptococcus pyogenes infections progress with extraordinary rapidity so that before an autogenous vaccine could be made the patient might have passed beyond the stage where vaccine therapy (or indeed any other treatment) would avail. On all who are well acquainted with vaccine therapy in such acute cases, the beneficial results following the administration of from one quarter to one million streptococcus pyogenes stock vaccine at the earliest possible moment in cases of erysipelas have made a great impression.

Streptococcus pyogenes vaccine finds a useful application in the following conditions :—

- (1) Erysipelas.
 - (2) Cellulitis and lymphangitis.
 - (3) Puerperal septicæmia.
 - (4) Acute surgical septicæmia.
 - (5) Phlegmasia alba dolens following childbirth or operation for mammary carcinoma.
 - (6) As a prophylactic measure before operation and especially when such operation involves the site of a healed septic wound.
 - (7) Septic wounds
 - (8) Paronychia
 - (9) Impetigo
 - (10) Septic burns.
- } either alone or combined with staphylococcus vaccine. (See Antisepsis Vaccine, page 36.)

The streptococcal origin of infections may very frequently be inferred, apart from bacteriological examination, by the clinical characteristics which they exhibit, *e.g.*, infections of the skin by itching or burning pain, by the diffusion of the inflammation and the copious exudation of nearly clear lymph, forming blisters beneath the intact epidermis or setting into amber yellow scabs when the epidermis has been injured; and open infections of deeper parts by the free discharge of thin serous pus.

In closed infections, *e.g.*, in the early stage of some cases of acute cellulitis before a bacteriological diagnosis can be arrived at, it is advisable to combine the minimum effective doses of Streptococcus and of Staphylococcus vaccines, and to repeat these after 24 or 48

hours, for by this means abscess formation may often be avoided. If, however, pus has already accumulated in quantity sufficient for detection, an incision should be combined with vaccine treatment.

As mentioned in connexion with staphylococcus vaccine it is usually preferable when the nature of a superficial infection is not clear, and where a bacteriological diagnosis cannot be established, to give a mixed vaccine of staphylococcus and streptococcus (*see* Antisepsis Vaccine) rather than either vaccine separately, as wounds or ulcers which have remained open for more than a day or two are nearly always infected with both of these organisms.

Great success has attended the use of the vaccine at St. Mary's Hospital in connexion with erysipelas, and several obstinate cases of recurrent infection have yielded in a very satisfactory manner. Ross and Johnston have published (*Journal of the Amer. Med. Assoc.*, March 6, 1909) a comparison between the records of 19 cases of erysipelas treated with vaccine at the General Hospital, Toronto, during 1908, and 19 other cases in the same hospital, but not so treated, during the preceding year. They found the average duration of pyrexia in these two groups to be respectively 3·1 and 8·9 days; the average duration of illness, 12·8 and 25·0 days; while complications of a serious nature are recorded as occurring in 1 of the inoculated cases as against 6 of the uninoculated.

Streptococcus Vaccine may also advisably be used (alone or in combination with Staphylococcus Vaccine) as a prophylactic measure against the septic infections which may follow upon surgical and obstetric operations and all kinds of wounds, in particular large superficial wounds, such as burns.

It has been found to be very efficacious as a prophylactic agent against septic infection following on operations which involve manipulation or section of scar tissue or adhesions resultant on a healed septic wound.

Viable streptococci have been recovered from such scar tissue or adhesions for many months after the healing of the wound, and it has been found that operations or manipulative procedures involving such areas have very frequently resulted in a flare-up of the streptococcal infection when the patient had not previously received two or three weekly injections of streptococcus vaccine.

Gay and Stone (*Journal of Infectious Diseases*, 1920, No. 26, p. 265) showed that in rabbits the empyema which was normally produced by the injection of 0·1 c.c. or 0·2 c.c. of a broth culture of streptococcus pyogenes into the pleura could be prevented by the previous immunisation of the animal to this bacterium.

Acute generalised streptococcal infections such as puerperal septicaemia are almost always due to streptococcus pyogenes, and much success has followed the administration of vaccine in these conditions. Western, at the London Hospital, in a large series of cases of puerperal

fever from all of which streptococci were isolated from the blood, obtained complete recoveries in about 50% of the patients treated with vaccine, whereas of the cases not treated with vaccine only about 10% recovered.

The less severe puerperal fevers, also, are usually caused by this microbe and respond readily to treatment with vaccine, provided the infected uterus is efficiently dealt with surgically, so that infected blood clots, etc., in which the streptococci can flourish out of reach of the anti-bacterial substances of the blood, are not retained.

This vaccine is issued in dilutions containing, respectively, 5, 20 and 100 millions of streptococci *per c.c.*

Dosage.—Minimum effective dose, 1 million; medium doses, 5 to 20 millions. For erysipelas, cellulitis, or other acute conditions a dose of 1 million may be administered, and 24 hours afterwards 2 millions may be given if the first dose has not given any "reaction." This may be sufficient to abort the acute stage of the infection, and the later dosage must be adjusted on general lines.

For less acute conditions 5 millions may be given as an initial dose, and this should be gradually increased every 4 to 10 days, provided no general reaction follows any inoculation.

ANTISEPSIS VACCINE (mixed *Staphylococcus* and *Streptococcus*).

This vaccine was primarily prepared for the treatment of superficial septic wounds and other septic conditions of the cutaneous and sub-cutaneous tissues in which, as is so often the case by the time the condition comes under the notice of the medical practitioner, a mixed infection of staphylococci and streptococci is present. In some cases the primary infection is a streptococcal one, as in paronychia or impetigo, and in other cases the primary infection is staphylococcal, as in sycosis or carbuncle, but very frequently after a few days both microbes are present and it is necessary to use a mixed vaccine of the two.

In the preparation of the vaccine the staphylococcus vaccine (*see page 29*) is mixed with streptococcus pyogenes and with other varieties of streptococci isolated from septic wounds in the following proportions:

<i>Staphylococcus aureus</i> and <i>albus</i> ...	...	...	...	...	1000 millions
<i>Streptococcus pyogenes</i> ...	...	...	...	...	20 millions
Other types of <i>Streptococci</i> isolated from septic wounds	...	...	...	...	30 millions

This vaccine is of especial value in superficial lesions in which the streptococcus and staphylococcus have established themselves. In almost all septic wounds or in superficial ulcers (whatever is the primary cause) it is usual to find an infection with both streptococcus and staphylococcus.

In paronychia and impetigo the primary infective agent is a streptococcus, but usually before the patient seeks medical advice a staphylococcal infection has become superimposed.

The vaccine is more suitable for the treatment of superficial septic lesions than is either staphylococcus or streptococcus pyogenes vaccine alone, and as it includes several varieties of streptococci of many different types it is more likely to be efficacious than is a simple mixture of these two vaccines.

Antisepsis Vaccine is indicated in the following conditions :—

- (1) Septic wounds.
- (2) Paronychia.
- (3) Impetigo.
- (4) Burns.
- (5) Pruritus ani.
- (6) Suppurating ulcers.
- (7) As a prophylactic measure before operations or after parturition. Three doses (0.5 c.c., 1 c.c., and 1 c.c.) may be given at weekly intervals as a prophylactic measure before surgical operations in which it is feared that septic complications may ensue. This prophylactic treatment is especially indicated in cases where the operation involves the region of the scar of an old septic wound.

Dosage.—For most conditions a dose of 0.2 c.c. will be a suitable initial dose, and this may be gradually increased every 4 to 10 days up to 1 c.c. if necessary, the dose being adjusted on the general lines laid down in the earlier pages.

PARODONTAL STREPTOCOCCUS VACCINE.

This vaccine is prepared from cultures of streptococci obtained from cases of pyorrhœa alveolaris.

The vaccine is issued primarily for use in connexion with cases of pyorrhœa, *i.e.*, in connexion with cases where the microbes of the mouth have invaded the gums and made their way down between these and the teeth, leading to the production of *pus*, the formation of *pockets*, the *loosening* and the *falling out of the teeth*, and the *retraction of the gums*.

The name 'parodontal' does not imply that the streptococci included in this group belong to any one definite type. It is merely a convenient name intended to include all the different types which are to be found associated with pyorrhœa alveolaris and other mouth infections. In infections of the buccal cavity, and among these pyorrhœa alveolaris takes a very prominent place, the dominant organisms are usually streptococci of various types, so that in the preparation of an efficient stock vaccine for use in the treatment of such infections it is necessary to incorporate many strains of different types isolated from such infections.

It is important, in connexion with the use of this vaccine, to remember that other microbes may be involved in the causation of a disease such as pyorrhœa alveolaris, and it is also most important not to forget

the ordinary surgical principles with regard to the evacuation of any accumulation of pus. Something may be done towards this end and towards the washing out of the pockets by inducing an increased outflow of lymph from the gums. This will be obtained by the use of a 0.5% sodium citrate and 5% sodium chloride solution.

The Parodontal Streptococcus Vaccine may be usefully applied also in connexion with other infections of the mucous membrane of the mouth and throat; in particular it has proved of service in the treatment of *small blisters and ulcers* of the mucous membrane of the tongue, cheeks and lips. Favourable results have also been obtained by the administration of the vaccine in cases where there was *toothache* due to trouble round the roots of the teeth; and it has also been brought into application in those cases of toothache which are associated with inflammation of the pulp cavity. There is reason to suspect that a streptococcus infection of the pulp may often be responsible for the causation of toothache.

The Parodontal Streptococcus Vaccine finds a further and very useful application in connexion with the treatment of *nausea* and of the *dyspepsias* which are associated with definite pyorrhœa, or with the slighter forms of infection which are indicated by *sponginess of the gums* and a red line round the margin of the teeth. It would seem that the nausea and dyspepsia which are so often a feature of phthisis may be associated with this microbic infection of the gums.

Lastly, the Parodontal Streptococcus Vaccine may usefully be employed in connexion with those cases of *rheumatism* which are associated with the presence of pyorrhœa. (*See also Anti-Rheumatic Vaccine, below.*) In typical cases of "pyorrhœic rheumatism" it will be found that the least overdose of the vaccine will aggravate the symptoms, while a small dose will be followed by a temporary amelioration.

This vaccine is issued in a dilution containing 30 millions of streptococci *per c.c.*

Dosage.—It would be well to begin, in cases of *mouth infections*, with a dose of 6 millions, and it will rarely be necessary to increase the dose beyond 10 millions. In cases of "*pyorrhœic rheumatism*" it is well to begin with a dose of not more than 3 millions.

ANTI-RHEUMATIC VACCINE.

Description.—This vaccine is prepared from cultures of numerous strains of streptococci isolated from the mouth, intestine and genito-urinary tract of patients suffering from rheumatism and rheumatoid arthritis.

Many observers have shown that chronic rheumatism follows streptococcal infections of the mouth, intestine or genito-urinary

tract. Almost all cases show some pyorrhœa alveolaris, and most of them show a greatly increased streptococcal flora in the intestine. It is probable that with the long-continued swallowing of saliva from a mouth affected with oral sepsis some of the living streptococci pass into the intestine and flourish there, and it is common in "rheumatic" people to find "mouth" types of streptococci in large numbers in the fæces. The streptococci which infect the gums and the intestine are usually of the non-hæmolytic variety and are not so pathogenetic as the hæmolytic streptococci which are responsible for erysipelas, cellulitis, broncho-pneumonia or acute septicæmia. They produce a chronic infection which if untreated may have most distressing results in crippling the individual.

Dosage.—The vaccine is issued in five dilutions containing respectively 5, 20, 50, 250 and 500 million streptococci *per c.c.* In the average case of chronic rheumatism or rheumatoid arthritis it is recommended that doses should be given at weekly intervals, commencing with 5 millions and gradually increasing, provided no general reaction is noted, up to 500 millions, if necessary. Usually something like a 50% increase in each dose furnishes a suitable graduation. If, however, the patient is doing very well on the smaller doses it is wise to make the increase smaller or to repeat the same dose several times.

If a *general* reaction (exacerbation of the rheumatism, fever or malaise) should follow any injection of the vaccine, the next dose should be delayed for one week and should be slightly smaller than the one which induced the reaction. For doses of over 50 millions a proportionate quantity of the more concentrated vaccines should be used to avoid the administration of too great a bulk of vaccine.

Therapeutic Indications.—This vaccine is primarily adapted for the treatment of cases of chronic rheumatism, under which term is included rheumatoid arthritis, fibrositis and some forms of neuritis. As the streptococci which have been isolated from the blood or valvular lesions in cases of rheumatic fever are similar in character to those incorporated in this vaccine its administration is also suggested in this condition.

Results.—It must be clearly understood that to obtain a good result the vaccine treatment must be persisted in for a considerable time. Where there is an active infection of the mouth or intestine the vaccine by itself cannot be expected to effect a cure, and dental treatment must be carried out, while at the same time constipation must be prevented.

Usually the first effect of a vaccine is a very marked and early decrease of the depression which is such a common feature of the disease, so that even before any improvement in the rheumatic

condition itself is manifest the patients feel that they are receiving benefit from the injections. Ultimately, in a large proportion of the cases the symptoms disappear, although where there is much deformity this will persist.

INTESTINAL STREPTOCOCCUS VACCINE.

This is prepared from a large number of different strains of streptococci isolated from the fæces of many patients who showed an enormous preponderance of streptococci in the intestine, and who were suffering from various forms of intestinal toxæmia.

While this vaccine may be of the greatest use in the treatment of some cases of intestinal toxæmia, it has to be kept in mind that poisoning from the intestine is not wholly caused by the streptococcal group of microbes and that there are many bacilli of the coliform group which may in many cases play the leading rôle. These are of so varied a character that it is not practicable in the light of our present knowledge to prepare a mixed stock vaccine from them. A vaccine such as this Intestinal Streptococcus Vaccine (*see* Intestinal Infections, page 62) is not intended to replace the careful bacteriological examination of the stools and the preparation of an autogenous vaccine of whatever bacterium happens to be the infecting agent. From a practical point of view, when a bacteriological examination of the stools is made, so much work is done in finding the infecting organism, and the labour involved in preparing an autogenous vaccine is so small in comparison, that it is better to prepare such a vaccine than to use any stock vaccine. This vaccine of intestinal streptococci is, however, intended for use in such cases as are suspected to be suffering from an intestinal toxæmia due to streptococci, and in which it is for some reason not practicable to make a complete bacteriological examination.

If it is suspected that *B. coli* is associated with the streptococcus in the toxæmia, this vaccine may be combined with the Mixed Vaccine for Coliform Infections (*see* page 65).

Dosage.—This vaccine is sent out in strengths of 2, 10, 50, and 500 millions *per c.c.*, so that a wide range of dosage may be used. It is recommended that an initial dose of 5 millions be given, and this should be increased by about 50 per cent. every 4 to 7 days up to, if necessary, 500 millions. As with other vaccines, however, if the clinical condition appears to be improving rapidly with any given dose this should be repeated several times without increase, and the subsequent increases should be slow, otherwise there is a danger of increasing the dose beyond the optimum for the particular patient. Again, if any general reaction should be induced by any dose, the next dose should be reduced and the subsequent increases should be very gradual.

The dilution containing 2 millions *per c.c.* is specially provided for use in cases of asthma where it is concluded that the asthma is due to a streptococcal infection of the intestine. For the use of the vaccine for this purpose the reader is referred to page 89 where the question is fully discussed.

VACCINES FOR PROPHYLAXIS AND TREATMENT OF INFLUENZA, COMMON COLDS, NASAL AND BRONCHIAL CATARRH, ASTHMA, PNEUMONIA, ETC.

In no conditions will the physician obtain better results with vaccines than in catarrhal conditions of the respiratory tract.

These catarrhal conditions are due to infections with one or more of the following organisms :—Pneumococcus, Streptococcus, Pfeiffer's Bacillus of influenza, Micrococcus catarrhalis, *B. septus*, *B. pneumoniae* of Friedländer, and Staphylococcus. Sometimes the infection is a simple one, but more usually two or more of these microbes are implicated. For simple infections with Pneumococcus or Pfeiffer's Bacillus of influenza the vaccines of these organisms may be used (*see* pages 49, 48), but where other microbes are associated, as they usually are, then mixed vaccines may be employed with advantage. Frequently it is impossible to make an accurate diagnosis of the infective agent rapidly in the initial stages of an infection, and as this is the most valuable period for the use of vaccines, it is of great assistance to give a mixed vaccine of these catarrh-causing microbes at the earliest possible moment, without waiting for the bacteriological diagnosis. In this way many acute infections can be aborted.

Common Cold ; Coryza ; Rhinitis.

All the microbes enumerated above may be isolated at one time or another from patients suffering from "colds." The most commonly found microbes are, however, Pneumococcus, Pfeiffer's Bacillus, Micrococcus catarrhalis and Bacillus septus. The predominance of one or other of these varies in different localities and at different times. Thus at one period an epidemic of "colds" in one place may show a great predominance of Pneumococcus, while in another place at the same time *B. septus* or Micrococcus catarrhalis may be predominant, although a second epidemic at the first place may show *B. septus* and at the second place Pneumococcus.

Two vaccines are sent out containing all these microbes. One—Anti-Catarrh Vaccine—is intended primarily for prophylactic use, while the other—Mixed Vaccine for Colds—is designed for use in treatment.

Chronic Bronchitis.

In this condition the microbes most commonly implicated are Pfeiffer's Bacillus of influenza, Pneumococcus and Streptococcus,

although any of the other microbes noted above as occurring in respiratory infections may be found.

Vaccine treatment will usually be found to be of extreme value in bronchitic conditions, whether acute or chronic. If the infection is a single one a simple vaccine may be used, but if, as is often the case, the infection is multiple, then a compound vaccine should be employed. If facilities are not at hand to establish a bacteriological diagnosis it is, as a rule, wiser to employ a compound vaccine, such as Mixed Vaccine for Colds or Anti-Catarrh Vaccine (in small doses). The doses of each are indicated in connexion with the separate vaccines.

Asthma.

The pathology of this condition is by no means definite; it is clear, however, that some types of spasmodic asthma definitely come within the group which Freeman has termed "Toxic Idio-pathies," certain food idiosyncrasies, animal asthmas, pollen fevers, etc., being caused by foreign proteins. In bronchial asthma, where the disease is bacterial in origin, very good results have frequently followed the use of the Mixed Vaccine for Bronchial Asthma.

Influenza.

There is still considerable controversy as to what is the primary infective agent in this epidemic disease. It is clearly established, however, that the serious or fatal complications such as bronchitis and pneumonia, as well as many of the less serious symptoms, are caused by the same organisms that have been found in chronic bronchitis, namely, Pfeiffer's Bacillus of influenza, Pneumococcus and Streptococcus, and it has been shown that a mixed vaccine containing these organisms is of extreme value both as a prophylactic and as a curative agent.

In October, 1918, the Army authorities decided to issue a prophylactic vaccine containing a mixture of Pfeiffer's Bacillus, Pneumococcus and Streptococcus (Original Army Formula—see page 48). Sir William Leishman has reported the results obtained with this vaccine in various camps in England (*Lancet*, Feb. 14, 1920). These results are summarised in the following table, from which it will be seen that by means of the vaccine the incidence of influenza was reduced to one-third, while the case mortality was reduced to almost one-twentieth of the mortality of the uninoculated cases.

Strength.				Incidence of Attack.	Incidence of Pulmonary Complications.	Incidence of Deaths.
Inoculated ...	...	...	5,624	14.1	1.6	0.12
Non-inoculated ...	...	...	43,520	47.3	13.3	2.25
				Ratios per 1,000.		

This vaccine was considered to contain too small a dose of the various microbes, and in 1919 the Mixed Anti-Influenza Vaccine (St. Mary's Hospital Formula) was introduced, which contains a larger dose of the various microbes and which is considered by the authorities at the Inoculation Department, St. Mary's Hospital, to be the most suitable for prevention of influenza and its complications. There is reason to hope that the statistical results of its use will be even better than the figures given by Sir William Leishman in connexion with the original Army Formula.

Good results have also followed the administration of a simple Influenza Bacillus Vaccine, or of the Mixed Vaccine for Colds, or the Anti-Catarrh Vaccine.

DOSAGE OF POLYVALENT "ANTI-CATARRH" AND "ANTI-INFLUENZA" VACCINES.

Prophylaxis.—It is recommended that in prophylactic inoculation against influenza, bronchial and nasal catarrhs, etc., for adults and young people over 16, the doses of the various mixed vaccines should be $\frac{1}{4}$, $\frac{1}{2}$ and 1 c.c. at intervals of a week to 10 days. Where patients are very susceptible to catarrhal attacks further injections of 1 c.c. may be given at monthly intervals throughout the winter. In any case, it must be remembered that the immunity conferred lasts only about three months, and at the end of that time another dose of 1 c.c. should be given. This in most cases suffices to give a fair measure of protection during the winter, but the next autumn the three doses of $\frac{1}{4}$, $\frac{1}{2}$ and 1 c.c. should be repeated in susceptible persons. It is important to administer these doses before the winter sets in, so that immunity may be established before the patient runs much risk of infection with the catarrhal organisms.

For children the following scale may be adopted :—

For children between 10 and 16, give two-thirds of the adult doses.			
" " 7 and 10, give one-half	"	"	"
" " 2 and 7, give one-third	"	"	"

In order to guard against undue reactions, we have introduced sets of three graduated doses of Anti-Catarrh Vaccine and S.M.H. Vaccine for prophylaxis. In each case the three doses contain the equivalent of $\frac{1}{4}$, $\frac{1}{2}$ and 1 c.c. of vaccine.

In this connexion, however, it is necessary to emphasise that the different dilutions of the various vaccines are not to be regarded as graduated doses for routine use in all cases, but to enable the physician to obtain, with facility, minimum, medium and maximum doses, as indicated, in volume suitable for injection.

The amount of success to be anticipated as a result of the use of anti-catarrh vaccines as a prophylactic measure is dependent on several factors apart from the actual composition of the vaccine. The susceptibility of different individuals to catarrhal infections varies enormously, and it is a matter of common observation that while

some people are having attack after attack of nasal or bronchial catarrh during the winter others only rarely suffer. In some cases this is undoubtedly due to the so-called susceptible individual having a chronic catarrhal infection with one or more of the microbes which are found in these conditions. During the "quiescent" periods the infection does not obtrude itself and the symptoms are so slight that they are accepted as part of the normal course of events, although if a bacteriological examination is made the infection is obvious. This chronic infection has more or less frequent exacerbations which the sufferer labels as "colds." The treatment of such a condition must vary from that of the next class of sufferers, who although they do not appear to have any constant infection, yet are so susceptible to infection with the catarrhal microbes that whenever they come into contact with a person suffering from a cold they promptly get infected.

In the case of the individual suffering from the chronic infection there is a very considerable risk, if the full prophylactic dose is given, of causing an exacerbation, and thus it is that there may be occasional complaints that the administration of the vaccine is followed immediately by a "cold." In such cases not more than half the first dose should be given, then after 5 to 7 days the whole first dose, then at weekly intervals doses of 0.35, 0.5, 0.75, and 1 c.c., the practitioner being guided, of course, in the later doses by the results of the earlier ones as laid down in connexion with dosage in general, p. 13. In this way the immunity can be increased and in a large number of cases the chronic infection will be eliminated or reduced to such a level that for a time it can be neglected. It is not, however, suggested that in all cases the immunity lasts in its full effective strength for more than three months; after that time the patient might have other two doses, one of 0.5 and the second of 1 c.c. As will be well understood, these suggestions for dosage are set forth to meet the ordinary case, but every now and again individuals will be met with for whom such a scheme will not be the most effective. In many such cases it will be found that the dosage suggested will be too high, but occasionally larger doses than those indicated will be required, and it must be left for the practitioner to deal with the exceptional case when he may meet it.

With regard to the patient who shows an increased susceptibility to colds without showing any signs of chronic infection, it may also be found that the first dose of vaccine may be followed by a "cold," but in this case it will only be so if at the same time the patient has come into contact with an infected individual. In most cases, however, the ordinary dosage suggested is suitable and effective. If it is found that for any particular patient the dosage is too high, it should be noted, so that when the next course of vaccine is given the dose can be adjusted to suit the requirements.

Note on Carriers.

There is no doubt that among the general population there are large numbers of carriers—that is, people who carry in their throats or noses the various microbes which are associated with respiratory catarrhal conditions without themselves suffering more than a trifling inconvenience. In the case of those people, just as in the case of the individuals suffering from a chronic infection, it may be that the injection may wake these microbes up to activity, and so a “cold” may follow the injection of vaccine. In such cases the treatment should be on the lines suggested above in connexion with the patient with a chronic infection.

In a certain number of cases every year it is reported that the Anti-Catarrh Vaccine, which is the one in most common use for the prevention of colds and catarrhal conditions, has failed to afford adequate protection to the individual. Such cases are comparatively few, and it may be that they are explained to some extent in the above remarks on chronic infections and “carriers.” It should be borne in mind also that if the Anti-Catarrh Vaccine does not prove effective in any particular patient there are other vaccines which may yet be efficacious, and it has often been proved, especially when it is desired to prevent attacks of *bronchial* catarrh, that the Mixed Anti-Influenza Vaccine may be very effective, more so even, sometimes, than the Anti-Catarrh Vaccine. The Mixed Anti-Influenza Vaccine, however, only contains three of the microbes which may be found in these conditions, but those three are the most common and are certainly responsible for over eighty per cent. of the bronchial catarrhs. If, therefore, it should be found that the Anti-Catarrh Vaccine is in any particular patient not effective, and if following its administration there appears to be nothing in the nature of a reaction (or if its administration is followed immediately by a “cold”), it might be of advantage to try next time the Mixed Anti-Influenza Vaccine.

It must not be expected that in all cases the vaccines will confer complete immunity. Even if a very satisfactory degree of immunity be attained, it is always possible that the patient may meet with a large and virulent infection which will be able to establish itself, or, as a result of excesses or of neglect of the ordinary rules of health, he may temporarily render himself susceptible. Even in such cases, however, the attacks should be less severe and of shorter duration.

Treatment.—All these vaccines may be used in the treatment of influenza and its complications, as well as all catarrhal infections of the respiratory tract. In the use of these vaccines for treatment it must be borne in mind that the doses must be much smaller than those used for prophylaxis, and also that, although no hard and fast rule can be laid down in general, the more acutely ill the patient is the less should be the dose. Both for influenza and catarrh there are

issued two mixed vaccines (for influenza, the weaker "Original Army Formula" and the stronger "St. Mary's Hospital Formula;" and for catarrh, the weaker "Mixed Vaccine for Colds" and the more concentrated "Anti-Catarrh Vaccine"), and it is well to start the treatment of an acute case with about 0.1 c.c. of the weaker vaccine. This can be repeated, if necessary, in 24 hours, or a dose of 0.2 c.c. may be given if the first dose seemed to be too small. Further doses must be administered on general lines.

In the more chronic cases 0.1 c.c. of the more concentrated vaccine may be given to begin with, but even in these cases it is usually wise to commence with 0.1 c.c. of the weaker, and often it is unnecessary to increase the dose to more than 0.5 c.c. of this vaccine before the condition has cleared up.

In selecting the vaccine for use it must be remembered that if nothing is known of the nature of the infection, the "Mixed Vaccine for Colds" or the "Anti-Catarrh Vaccine" should be used.

ANTI-CATARRH VACCINE.

This vaccine is prepared from cultures of the various organisms which may cause nasal or bronchial catarrh, and is of great value as a prophylactic in persons susceptible to these infections.

It may also be used in treatment, but in that case the initial dose should not exceed 0.1 c.c., and it is usually more convenient to use the less concentrated Mixed Vaccine for Colds for this purpose.

It has been found that in some people the Anti-Catarrh Vaccine formerly supplied has given rise to considerable reactions. With a view to obviating these reactions without impairing the protective power of the vaccine the formula has been revised and reconstituted. Much of the reaction has been found to be due to the staphylococcal element of the vaccine, and this has been eliminated from the vaccine. Although staphylococci are frequently found in the nose in cases of chronic catarrh they play little part in the acute catarrhs against which the Anti-Catarrh Vaccine is designed to protect. The old formula is, however, still kept in stock should it be desired.

Minor alterations have also been made, as a result of long experience, in the proportions of the other constituent microbes. Each c.c. of Anti-Catarrh Vaccine now contains :—

M. catarrhalis	...	...	50 millions	B. septus	...	...	...	50 millions
B. pneumoniae	...	...	50 millions	B. influenzae	...	...	...	250 millions
Pneumococcus	...	...	250 millions	Streptococcus	...	...	...	25 millions

Dosage.—Three doses should be given at 7-day intervals, namely 0.25 c.c., 0.5 c.c., and 1 c.c., for which sets of 3 graduated doses are supplied. In persons who are very susceptible to "colds" or "catarrhs" during the winter months these injections should be given in the autumn, and during the winter a dose of 1 c.c. may be given each month. A scale of doses for children is given on page 43.

MIXED VACCINE FOR COLDS AND OTHER RESPIRATORY CATARRHS.

As a result of long-continued experience of these vaccines the formula of the Mixed Vaccine for Colds and other Respiratory Catarrhs has been revised and reconstituted with the object of giving a rapid rise in the immunity and at the same time minimising the danger of any reactions following its administration.

Each c.c. of the vaccine now contains :—

Pneumococcus	...	...	50 millions	B. septus	...	...	...	25 millions
B. pneumoniae	...	...	25 millions	B. influenzae	...	...	...	50 millions
Staphylococcus	...	...	200 millions	Streptococcus	...	...	...	10 millions
M. catarrhalis	...	...	25 millions					

Inoculation of this vaccine is intended to cut short "common colds" and other catarrhal conditions of the respiratory tract by evoking an immediate and adequate immunising response in the early stages of the infection.

With this end in view, and in order to avoid the necessity for a preliminary bacteriological examination of each case, the vaccine has been prepared from cultures of the several microbic species which are most commonly responsible for the malady. The representation of each of these constituent cultures has been so adjusted that a minimum effective dose of the Mixed Vaccine when employed, let us say, for a pneumococcal "cold," shall provide the quantity of pneumococcus vaccine appropriate for an acute infection by that microbe, and shall exercise no effect upon the patient by virtue of the other cultures, *e.g.*, of staphylococcus, streptococcus, etc., embodied in the dose, since these also are represented by the minimal effective quantities for the corresponding infections—quantities quite innocuous to individuals free from such infections. (For dosage see page 46.)

This vaccine has also proved extremely valuable in the treatment of bronchitis, and it has been used for a number of years as a routine in the treatment of this condition among the out-patients at the Inoculation Department, St. Mary's Hospital.

Mixed Vaccine for Colds is no longer supplied in graduated doses, since this vaccine is used for treatment only, and there is a risk of too large a dose being given by the issue of sets of graduated doses.

MIXED VACCINE FOR BRONCHIAL ASTHMA.

Patients suffering from bronchial asthma are usually infected with one or other of the microbes which are to be found in catarrhal conditions of the respiratory tract. The asthmatic condition, however, is due to some special hypersensitiveness to the proteins of the micro-organism or to the products of its metabolism rather than to the mere infection. These patients therefore are, as a rule, very sensitive to vaccines, and it has been found that the best results are obtained when the treatment is commenced with very small doses. Good results have been obtained with a very weak vaccine containing the various

microbes which are found in respiratory catarrhal infections. The composition of the vaccine is similar to that of the Mixed Vaccine for Colds and other Respiratory Catarrhs, but the strength is about 1-5th of that vaccine.

Each c.c. contains :—

M. catarrhalis	...	...	5 millions	B. septus	...	...	...	5 millions
B. pneumoniae	...	...	5 millions	B. influenzae	...	...	...	10 millions
Pneumococcus	...	...	10 millions	Streptococcus	...	...	...	2 millions
Staphylococcus	...	...	40 millions					

Dosage.—The first dose should be 0·2 c.c., and the doses may be increased, if there is no sign of any reaction, by 0·1 c.c. every 3 to 7 days up to 1 c.c. If larger doses are required the Mixed Vaccine for Colds should be used, but it must be remembered that 0·2 c.c. of the Mixed Vaccine for Colds is equal to 1 c.c. of the Mixed Vaccine for Bronchial Asthma.

MIXED ANTI-INFLUENZA VACCINE (St. Mary's Hospital Formula.)

This formula is the one which the authorities at the Inoculation Department, St. Mary's Hospital, consider the most suitable for the prevention of influenza and its complications.

Each c.c. of the vaccine contains :—

B. influenzae	...	...	...	...	...	500 millions
Pneumococcus (mixed types)	...	...	...	...	...	1,000 millions
Streptococcus (mixed types)	...	...	...	...	...	100 millions

Supplied in 1 c.c. ampoules and 25 c.c. bottles, and also in sets of 3 graduated doses corresponding to $\frac{1}{4}$, $\frac{1}{2}$ and 1 c.c. of the vaccine.

Dosage.—For general directions as to dosage, see page 43.

ANTI-INFLUENZA VACCINE (Original Army Formula.)

This vaccine is prepared in accordance with the formula decided upon at a conference held at the War Office (see *British Medical Journal*, October 26, 1918, p. 470). Each c.c. of the vaccine contains :—

B. influenzae	...	...	...	...	...	60 millions
Pneumococcus (mixed types)	...	...	...	...	...	200 millions
Streptococcus (mixed types)	...	...	...	...	...	80 millions

Dosage.—For general directions as to dosage, see page 43.

INFLUENZA BACILLUS VACCINE.

This vaccine is prepared from cultures of the influenza bacillus (Pfeiffer) isolated from cases of acute epidemic influenza, chronic bronchitis, and other infections of the respiratory tract.

It must be borne in mind that the clinical picture of acute influenza is often reproduced more or less closely by infections other than those by the "influenza bacillus," and that, on the other hand, many cases of infection with this bacillus have none of the clinical features of acute influenza. Pfeiffer's bacillus is a common infective agent in chronic bronchitis (frequently associated with asthma), chronic rhinitis or sinusitis, and it has been shown to be present in a very large number of cases of whooping cough and in bronchitis or broncho-pneumonia following measles. It is as yet uncertain whether or not Pfeiffer's bacillus is the primary infective agent in

acute epidemic influenza, but it has been established that practically all the cases of this condition rapidly become infected with it, and that it is largely responsible for the pneumonia to which the fatal results are due. Only rarely, however, is Pfeiffer's bacillus the only infecting agent in post-influenzal conditions, and it is usually associated with pneumococci or streptococci.

Fleming and Clemenger (*Lancet*, Nov. 15, 1919) have shown that animals immunised with one strain do not as a rule produce antibodies to more than a small proportion of the other strains. To overcome this extreme specificity there has been incorporated in the Influenza Bacillus Vaccine (as well as in the compound influenza vaccines) a very large number of strains of the bacillus. Thus it has an extremely wide polyvalency.

Dosage.—In the prophylaxis of acute epidemic influenza good results have been obtained by some observers from the use of a pure influenza bacillus vaccine, although the vaccine most commonly employed for this purpose has been the mixed influenza vaccine (see page 41 *et seq.*). For this purpose the dosage employed has been 500 millions to commence with, followed in 7 to 10 days by 1,000 millions.

For the treatment of acute influenzal conditions 25 millions may be given as an initial dose, and this dose may be doubled after 24 hours provided the temperature does not come down. Further doses may be regulated on general lines by the result of the first injections.

In chronic cases it is advisable to commence with 25 millions, and to increase the dose by 50% every week until the full dose of 500 millions is reached, provided there is no general reaction following any of the injections. If a general reaction occurs, the next dose should be cut down by half and the subsequent increases in dosage should be very gradual.

The vaccine is issued in three dilutions, containing 100, 500 and 1,000 millions *per c.c.*

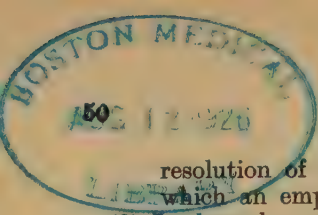
PNEUMOCOCCUS VACCINE.

The pneumococcus is a microbe which has derived its name from its being in most cases the infective agent in lobar pneumonia. In addition to its pathogenic properties in this respect, however, it is very commonly found in catarrhal infections of the respiratory tract, either of an acute or of a chronic character.

This vaccine is prepared from cultures of pneumococcus isolated from cases of croupous pneumonia, bronchitis, the common cold and other types, and it contains representatives of the different immunological types into which pneumococci have been divided.

It is indicated in the following conditions:—

- (1) In lobar pneumonia, in the very early stages before consolidation of the lung is extensive and in protracted cases in which



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resolution of the pneumonic exudate has been delayed or in which an empyema has developed.

- (2) In broncho-pneumonia, where this is demonstrated to be a pure pneumococcus infection.
- (3) In bronchitis, acute and chronic, when pneumococcus is the infecting agent.
- (4) In some cases of "common colds," when pneumococcus is the infecting agent.
- (5) In rhinitis, tonsillitis or laryngitis, when pneumococcus is the infecting agent.
- (6) Certain catarrhal ophthalmias and corneal ulcers, when pneumococcus is the infecting agent.
- (7) As a prophylactic measure against lobar pneumonia.

Of 43 cases of lobar pneumonia treated with vaccine at St. Mary's Hospital in 1909 and 1910, only one patient died of the disease (one other died with symptoms of nephritis), and, for the rest, very satisfactory results were obtained. (Willcox and Parry Morgan, *B.M.J.*, October 9, 1909, and Parry Morgan, *Proc. Roy. Soc. of Med.*, Vaccine Therapy debate, 1910, vol. iii.)

Wright and his colleagues found in connexion with vaccination against pneumonia in South Africa that the vaccine when given in the incubation period seemed to abort the disease. They also found that the incidence of, and the mortality from, lobar pneumonia were markedly diminished by the prophylactic inoculation of two doses of *Pneumococcus Vaccine* in doses of from 300 to 600 millions. Their work in South Africa was done before the pneumococci were shown to fall into several different serological groups, and Lister, who continued the prophylactic inoculation against pneumonia in South Africa, and who used a vaccine which was representative of the various types infecting the natives, obtained even better results.

The following table gives the results obtained at the Premier Diamond Mine:—

PNEUMONIA RETURNS FOR THE YEARS 1908-1913. ALSO OF THE PERIOD FROM NOVEMBER, 1916, TO OCTOBER, 1917, INCLUSIVE.

Year.	Incidence per 1,000.	Mortality per 1,000.
1908	70-71	14-17
1909	104-85	17-97
1910	153-54	28-97
1911	128-98	26-94
*1912	67-68	19-96
*1913	31-75	4-80
†1914	—	—
†1915	—	—
Experimental period: Nov. 1916 to Oct. 1917	4-67	0-86

* During these years, the inoculations were carried out in accordance with the principles advocated by Sir Almroth Wright and his associates.

† No record, on account of war conditions.

During the late war, prophylactic vaccination against pneumonia was carried out on a large scale in the various United States Army base camps. In most cases three doses were given, and it was found that the incidence of pneumonia was reduced to less than half, and the mortality was even more strikingly reduced.

For prophylaxis against lobar pneumonia the best results have been obtained with doses of from 500 to 5,000 millions.

Pneumococci are responsible entirely or in part for a very large proportion of the acute and chronic infections of the nose, larynx and bronchi, and a pneumococcal vaccine gives extremely good results in these conditions. The pure pneumococcus vaccine should be used when the infection is a simple one. When the infection is a mixed one it will be more efficacious to use one of the compound vaccines (*see later*).

The vaccine is issued in dilutions containing 20, 50 and 200 millions of pneumococci *per c.c.*

Dosage for Treatment.—Minimum effective dose, 10 millions; medium doses, 20 to 30 millions. In the case of pneumonia an appropriate initial dose would be 20 millions. Where that dose brings down the temperature it may with advantage be repeated in two or three days, the curve of the opsonic index, or, in default of this, the curve of the temperature, being here taken as a guide. If the initial dose of 20 millions leaves the patient's condition unaltered, a further dose of 30 millions may with advantage be administered next day.

In average cases of acute or chronic pneumococcal bronchitis an initial dose of 15 to 20 millions is recommended.

WHOOPIING COUGH VACCINE.

Bordet and Gengou, in 1906, described a bacillus which they claimed to be the causative agent in whooping cough. This bacillus, which was of somewhat the same nature as the influenza bacillus of Pfeiffer, could only be isolated on a special medium which they described, and it could only be isolated in the first few days of the disease; after that time cultures revealed only secondary infections of which the most notable were the influenza bacillus of Pfeiffer and the pneumococcus. Bordet's observations on this bacillus have been confirmed from many parts of the world.

Three different vaccines are sent out for the prevention or treatment of whooping cough. For prophylaxis there are two vaccines, one containing only Bordet's bacillus and the other containing in addition pneumococcus and the influenza bacillus. Although these last two organisms are only secondary infecting agents, it is probable that much of the misery of whooping cough is due to them, just as the most serious complications of influenza are due not to the primary infection but to the superadded secondary infecting organisms.

The composition of these vaccines is as follows :—

Whooping Cough Vaccine, "A," Prophylactic.

Bordet's Bacillus 4,000 millions per c.c.

Whooping Cough Vaccine, "B," Prophylactic.

Bordet's Bacillus 4,000 millions per c.c.
Pneumococcus 100 " "
B. influenzae (Pfeiffer) 500 " "

With either vaccine three doses should be given at intervals of four days, according to the following scale :—

	1st Dose.	2nd Dose.	3rd Dose.
	c.c.	c.c.	c.c.
Up to 1 year	0.1	0.2	0.4
1 to 2 years	0.2	0.4	0.8
3 to 5 years	0.3	0.6	1.0
5 to 10 years	0.4	0.8	1.0
Above 10 years	0.5	1.0	1.0

There is apparently very little reaction following the inoculation of this bacillus.

Graham and Hess (quoted by Shaw, *Amer. Jour. of Obstetrics*, 1917) showed that of 164 children inoculated in one institution only 7% contracted the disease during four epidemic periods, whereas prior to the introduction of prophylactic inoculation about 50% of the children contracted the disease during each epidemic. These children had received three doses of a simple Bordet Bacillus Vaccine. Their conclusion was that "the value of vaccines as a prophylactic measure is undeniable, and they should be administered to every child exposed to Whooping Cough."

Therapeutic Use.—In all cases it is desirable that a mixed vaccine should be used, as there is almost always secondary infection of Pfeiffer's Bacillus and Pneumococcus.

Freeman, of the Inoculation Department, St. Mary's Hospital (*Proceed. Roy. Soc. Med.*, 1910, vol. iii.), showed that the administration of vaccine to children suffering from whooping cough cut short the duration of the disease and proved itself of very definite value in the treatment. Children suffering from whooping cough are remarkably tolerant of this vaccine, so that it can be administered in comparatively large doses and at short intervals without inducing general or focal reactions.

Whooping Cough Vaccine "C" (for treatment) is issued in a dilution containing in each c.c. :—

Bordet's Bacillus 500 millions
B. influenzae (Pfeiffer) 250 millions
Pneumococcus 20 millions

and the doses recommended for a child of 5 or 6 years of age are as follows :—

0.2 c.c., 0.3 c.c., 0.5 c.c., 0.7 c.c., 1 c.c., and, if necessary, further doses of 1 c.c. The interval between the doses should be 2 or 3 days only. If, however, it should chance that the vaccine causes a general reaction, the next dose should be diminished by half and the interval lengthened to about a week.

GONOCOCCUS INFECTIONS.

It may be frankly stated that no specific treatment has yet been evolved which will rapidly and completely clear up gonorrhœal infections. There is, however, abundant evidence that Bacterial Vaccines, properly prepared and intelligently used, will accomplish a great deal, not only in the complications and sequelæ of gonorrhœa, but even as adjunctive treatment in the acute stages of the disease.

In acute gonorrhœa, vaccine treatment by itself will not produce a very obvious result, but it must be remembered that gonococcus vaccine like the other vaccines acts by increasing the content of antibodies in the general circulation, and there is abundant evidence, as the result of experiment on man and animals, that the administration of gonococcus vaccine does so increase the antibody content of the blood.

Although for some local reason this increase of the general resistance does not immediately have a very striking effect on the course of the infection, yet it stands to reason that it must have an effect in limiting the infection and thus tend to prevent its spread from the urethra to other structures whether they be in the neighbourhood, such as the bladder or the epididymis, or more distant areas such as the joints. The initial impetus given to the patient's immunizing defence by the prompt employment of a suitable vaccine in an acute case may be the deciding factor in preventing some serious complication.

The value of vaccine therapy as adjunctive treatment in the less acute types of gonorrhœal infection, such as chronic urethritis, epididymitis, prostatitis, and orchitis, is pretty generally accepted. Bacterial immunization in these cases is unquestionably a very valuable measure. In gonorrhœal arthritis also such therapy often affords striking results.

While the gonococcus is wholly responsible for gonorrhœa in the early stages of the infection, in chronic conditions where the case does not clear up, there are frequently other organisms which seem to play a part in the infection. Thus, in the cases of chronic gleet it is common to find in addition to the gonococcus, staphylococci, streptococci, or diphtheroid bacilli, and these may keep up a chronic catarrhal infection even after the gonococcus has disappeared. In some cases, also, in which the gonococcus has undoubtedly induced an arthritis, this seems to be carried on later as a chronic infective condition by the other organisms which may have gained access to the urethra and, more especially, the prostate gland. The chief among these secondary infections as regards the arthritis are streptococcal. For these chronic conditions a mixed vaccine is often found to be advantageous.

GONOCOCCUS VACCINE.

This vaccine is prepared from cultures of gonococcus (Neisser) obtained from cases of acute urethritis. It is issued for use in the treatment of genito-urinary infections caused by this microbe, and the conditions associated therewith, gonorrhœal rheumatism, iritis, etc.

Acute Gonorrhœa.

Favourable results have been obtained in a good number of cases, and are to be expected when the patient will submit to a regimen of rest during the stage of acute inflammation.

If this condition is not fulfilled, excessive auto-inoculations are likely to occur, and will militate against a satisfactory response to the vaccine.

A small dose of Gonococcus Vaccine (2 to 5 millions) is appropriate during the acute stage of the disease, and should not be exceeded, lest a negative phase of immunity should be induced and opportunity be afforded for the spread of the infection to joints, epididymis, etc.

Such small doses should be repeated at intervals of two to three days, and may be cautiously increased, if necessary, after the acute symptoms have quite subsided.

Vulvo-vaginitis in children has been very successfully treated by Gonococcus Vaccine.

Hamilton (*Journal of Amer. Med. Assoc.*, 1910), in an analysis of 344 cases, found that the average duration of treatment in 84 inoculated cases was 1·7 months, as compared with 10·1 months for 260 children treated by irrigation. 90% of the inoculated were considered cured—the absence of gonococci in several successive examinations being taken as the criterion of cure. Six inoculations sufficed for the cure of most acute cases.

Butler and Long (*Journal of Amer. Med. Assoc.*, 1908, pp. 744 and 1301) also attempted a comparison of smaller groups of "vaccine" and "irrigation" cases, and obtained results similarly favourable to vaccine therapy.

Chronic Urethritis.

It frequently happens that an acute urethritis in its later stages gives place to a secondary infection of the urethral mucous membrane, e.g., by diphtheroid microbes or staphylococci or streptococci, and that in the discharge which persists under these conditions, few, if any, gonococci are to be found. In such cases, little benefit is to be expected from the employment of a simple Gonococcus Vaccine, and for the treatment of these conditions a Mixed Gonorrhœa Vaccine has been introduced containing in addition to the gonococcus all the secondary invaders enumerated above (see page 56).

Other cases, however, in which the gonococcus is still predominating in the discharges, may advisedly be treated with medium to large

doses at intervals of 7 to 10 days, and will often yield, although perhaps slowly, to this procedure.

The possibility of inducing undesirable negative phase phenomena, which was seen to call for caution in the treatment of acute gonorrhoea, need not be considered in connexion with very chronic cases.

Gonococcal Arthritis.

Gonococcus Vaccine has been extensively used, and with more striking results, in the treatment of this malady than in any other gonococcal infection.

The pain and swelling of "acute joints" have rapidly diminished, and recovery has been so much hastened that subsequent fixation by adhesions is either not produced or may be safely dealt with by manipulative procedures at an early date.

In the conduct of these acute cases, small doses (1 to 3 millions) will be found most suitable; larger ones should be avoided from a fear of precipitating an attack in unaffected joints.

With chronic arthritis it is usual for a temporary relief of symptoms to follow upon each suitable dose of vaccine, but complete recovery will be won more slowly than in the acute cases, and inoculations may have to be continued in some cases for a period of 6 to 12 months.

The doses appropriate to affections of this latter class will vary somewhat widely, ranging from 3 millions upwards to 25 or 50 millions, and the interval should be correspondingly increased, as larger doses are employed, to 7 or 14 days.

Some cases of "gonorrhoeal" rheumatism will benefit by the administration of the anti-rheumatic vaccine in addition to the gonococcus vaccine. This combination may succeed in cases where the gonococcus vaccine fails to give complete relief.

The following reports upon the vaccine treatment of gonococcal arthritis may be consulted:—

Eyre and Stewart (25 cases), *Lancet*, July 10, 1909.

Hartwell (51 cases), *Annals of Surgery*, Nov., 1909.

Jack (4 cases), *Glasgow Medical Journal*, 1910.

This vaccine also finds application in those cases, not uncommonly met with, in which vague pain persists for months or years after gonorrhoea, notably in the heels and in the back, upper arm and palms, without any external manifestation of disease.

Progress in these cases is usually gradual, but very definite, and the vaccine should be continued over a period of not less than 3 months, in doses of 10 millions and upwards, to effect a satisfactory cure.

Again, in affections of the eye *Gonococcus Vaccine* may sometimes be very successfully employed.

Eyre and Stewart (*Lancet*, July 10, 1909) have reported in detail 4 cases of gonococcal iritis treated at Guy's Hospital. They call attention particularly to the *prompt relief of pain* within 48 hours of the first inoculation of vaccine, and to the rapidity of the cure.

Successful cases of gonococcal ophthalmia are reported by Bryan (*Brit. Med. Journal*, March 23, 1912), and Rubbrecht (*Bull. de la Soc. Belge d'Ophthal.*, 27, 1909).

The plan of treatment suggested under acute gonorrhœa will be appropriate to this condition.

This vaccine is issued in dilutions containing 5, 20, 50, 200 and 500 millions of gonococci *per c.c.*

Dosage.—Summary.—Minimum effective dose, 1 to 5 millions; medium doses, 10 to 50 millions.

MIXED GONORRHŒA VACCINE.

This vaccine contains in addition to the gonococcus the several microbes which may secondarily infect the urethra.

Each c.c. contains :—

Gonococcus	...	...	...	...	...	...	...	500 millions
Staphylococcus	...	...	...	...	...	...	...	1,000 millions
Streptococcus	...	...	...	...	...	...	...	100 millions
Diphtheroid Bacillus	...	...	...	...	...	...	...	200 millions

In chronic gonorrhœa or gleet it is usual to find that the gonococci in the discharges are very few and that large numbers of streptococci, staphylococci or diphtheroid bacilli may be present. Such cases have been treated with considerable success with a mixed vaccine of these organisms.

Patients suffering from chronic gonorrhœa are very tolerant of gonococcus vaccine, and this vaccine contains a relatively large number of gonococci (500 millions *per c.c.*). In spite of this there is very little risk of a focal reaction following the administration of the vaccine.

This vaccine is suitable for the treatment of gleet or chronic prostatitis of gonorrhœal origin in men, or chronic gonorrhœa in women.

Dosage.—The initial dose should be 0.2 c.c., and this should be gradually increased at weekly intervals, provided there is no reaction, until a dose of 1 c.c. is reached.

TUBERCULAR INFECTIONS.

In cases of tubercular infection it is desirable to regulate the dosage by means of the opsonic index so as to adjust the treatment to the requirements of the individual case; but where this cannot be carried out, tuberculin treatment may none the less be usefully embarked upon if the dosage is carefully regulated in accordance with the general instructions given in section 4, page 15, and if the treatment is confined to cases which comply with the conditions laid down above.

TUBERCLE VACCINE. (Tuberculin. Bacillary Emulsion.)

The form of Tuberculin here in question is to be regarded as essentially comparable to other vaccines, being prepared from sterilised cultures of the Tubercle Bacillus (human type).

The method of standardisation of this vaccine—by weight of powdered bacillary substance *per c.c.* of emulsion—is adopted as alternative to the method of enumeration employed for the other vaccines, simply as an expedient of convenience.

This vaccine is issued principally for the treatment of localised tubercular infections. It should, however, be regarded as a *sine qua non* for the success of such treatment that the disease is not complicated by the occurrence of frequent auto-inoculations.

Such auto-inoculations may be suspected whenever the tubercular patient is found to be subject to irregular elevations of temperature, to headaches, undue fatigue and exacerbations of local symptoms—or their occurrence, and degree, may be detected with precision by estimations of the opsonic power of the patient's blood.

The course of all severe infections, and notably those of the lungs and joints, will be marked by these incidental occurrences, unless adequate conditions of rest—*e.g.*, by confinement to bed, restriction of exercise, or the splinting of affected joints—are imposed for their control.

Tubercular Glands.

Results excellent—large masses are often completely resolved by prolonged treatment, and the general health greatly improved.

The contents of “broken-down” glands should be evacuated by aspiration. In view of the possible presence of other foci of disease—especially in the bronchial glands in children—it would be well for the practitioner to commence treatment with a small dose, 1/50,000 to 1/25,000 milligram, and to increase it cautiously towards a medium effective dose.

The use of medium and large doses will sometimes determine the “breaking-down” of caseous glands.

Lupus.

Deep ulcerating lesions will usually heal very satisfactorily under treatment by medium and large doses of tuberculin, combined, when necessary, with the appropriate vaccines for secondary infections, *e.g.*, of staphylococcus, streptococcus, etc. These latter infections will frequently be found to play an important part in the process of ulceration, and should be suspected whenever the erosion of tissues is accompanied by purulent discharges, inflammatory reddening, oedema, etc.

X-ray or other "light" treatment may advantageously be employed in conjunction with vaccine therapy.

Little or nothing has been achieved by tuberculin treatment of *very superficial, non-ulcerative* lesions of lupus vulgaris, or of those of lupus erythematosus, probably owing to the deficient blood supply of the tissues in which these infections are seated.

Tubercular Peritonitis.

Results have been particularly good with small doses.

Genito-Urinary Tuberculosis.

Steady amelioration of local symptoms is the rule, along with a very satisfactory general condition. Large swellings of the epididymis have been almost completely resolved without resort to surgical extirpation. Minimal effective doses should be at first employed, and caution exercised in their increase—more particularly is this requisite in cases of tubercular cystitis, which are sometimes very susceptible to tuberculin. When the epididymis is alone involved, somewhat larger initial doses may be used, and the advance to medium doses more quickly effected.

A long course of treatment, 1 to 3 years, should be anticipated, and secondary infections also dealt with, should they occur.

Tuberculosis of Bones and Joints.

Good results, quickly obtained by comparison with other methods, are to be expected when tuberculin therapy is combined with effective splinting and rest; particularly if treatment is undertaken prior to the formation of sinuses, and this eventuality zealously avoided by the careful aspiration of abscesses.

Phlyctenular Conjunctivitis.

Initial doses should not exceed 1/150,000 milligram, and should be slowly increased. When so treated very favourable results are obtained.

Phthisis.

The employment of Tuberculin in the small doses here recommended has given good results in a very fair percentage of cases treated in London, and not a few of these cases have remained in good health for a period of years since treatment was discontinued.

Better results are to be expected where the treatment can be carried out for a long period in conjunction with sanatorium routine. Bearing in mind that the physical conditions in a tuberculous lung lend themselves very readily to auto-inoculation, and also the instructions relating to dosage embodied in section 4, page 15, the following general recommendations may be formulated:—

(1) Fever is to be regarded as an indication, not so much for the administration of Tuberculin as for rest; a curtailing, in some measure, of the daily exertions.

(2) When by this means the process of auto-inoculation has been eliminated, the aim of treatment should be to elicit a succession of small immunising responses by minimal doses, 1/500,000 to 1/100,000 milligram, at intervals of 3 to 5 days, and so to promote healing in and about the focus, or foci, of disease.

As this healing progresses, the doses may be cautiously increased, e.g., to 1/50,000 or 1/25,000 milligram, and the restriction of the daily exercise somewhat relaxed.

(3) Only in chronic conditions, and when exercise is well borne, will it be permissible to seek larger immunising responses by the employment of medium doses of Tuberculin, 1/10,000 to 1/5,000 milligram (at intervals of 7 to 10 days); and such doses should be at once reduced if followed by a definite rise of temperature, headache, etc.

(4) When bacteriological examination of the sputum affords evidence of a secondary infection, this should also be combated by the appropriate vaccine.

Tubercle Vaccine is issued in nine different dilutions, containing, respectively, 1/100,000, 1/40,000, 1/25,000, 1/10,000, 1/5,000, 1/2,000, 1/1,000, 1/500 and 1/100 milligram of powdered tubercle culture *per c.c.*

Dosage.—Summary.—Minimum effective doses for severe infections, 1/500,000 to 1/200,000 milligram; and for slight infections, 1/25,000 to 1/10,000 milligram. Medium doses, 1/10,000 to 1/4,000 milligram.

ACTINOMYCOSIS VACCINE.

This vaccine is prepared from cultures of the organism derived from several cases of human actinomycosis, and corresponding with that described and cultivated by Israel (1890) and by Homer Wright (1905). The mycelial threads of which such cultures are composed can readily be broken up into small fragments resembling bacilli, and by consequence the method generally employed for the standardisation of a vaccine—enumeration of its component units—is applicable also to this case.

The experience gained by the treatment of 23 cases of actinomycosis at St. Mary's Hospital has been summarised by Colebrook (*Lancet*, 1921, I., 893) as follows:—"The treatment of actinomycosis by vaccines facilitates recovery when efficient surgical drainage of the affected

tissues is secured and maintained ; when, however, drainage is unsatisfactory, the use of appropriate vaccines will not usually suffice to stay the progress of the infection." In other words, surgery should come first and vaccine therapy second in the treatment of this disease.

In the cervico-facial cases drainage can usually be obtained and a few doses of vaccine complete the cure. In the more severe cases which originate in the viscera of the thorax or abdomen the use of vaccine has sometimes given good results, and in view of the very grave outlook for such cases *it should certainly be tried at the earliest possible moment*. A favourable result of vaccine treatment in a similar but not identical type of infection was reported by Wynn (*British Medical Journal*, March 7, 1908).

Doses of actinomycosis vaccine ranging from 1 to 5 millions of mycelial fragments are recommended for the severe cases, and 5 to 20 millions for the less severe ones. And since it is found that the infection of actinomycosis lesions by other organisms exercises a very unfavourable effect upon the course of the disease, it is advisable, whenever bacteriological investigation has revealed the existence of such infections, to combat them by appropriate vaccines, *e.g.*, *Staphylococcus*, *Streptococcus*, concurrently with actinomycosis vaccine.

The vaccine is issued in a dilution containing 25 millions of mycelial fragments per c.c.

(It may be mentioned, as a matter of interest, that several cases of actinomycosis in young cattle have been successfully treated with this vaccine. For veterinary purposes a vaccine is issued containing 100 millions of mycelial fragments *per c.c.*)

ANTI-MENINGOCOCCUS VACCINE.

This is a polyvalent vaccine prepared from strains of different types of *Diplococcus intracellularis meningitidis* (Weichselbaum) isolated from cases of epidemic cerebro-spinal meningitis, and is issued for prophylactic use in connexion with that disease. It is supplied in a dilution containing 1,000 million meningococci *per c.c.*, for the prophylactic inoculation of individuals who may, or have, become exposed to infection from these microbes.

It is recommended that each such person shall be given by subcutaneous injection 500 million cocci for the first dose, and that ten days afterwards 1,000 millions shall be given for the second dose. Young children may be given, for the first injection, 2 to 5 minims (0.1 to 0.3 c.c.), according to age, and double that quantity ten days later.

Some local inflammation will frequently be caused by such prophylactic injections, but it will rarely be accompanied by any rise of temperature or definite malaise.

It is believed that the injection of Anti-Meningococcus Vaccine will prove valuable as a means of immunisation against epidemic cerebro-spinal meningitis, and that even should the disease manifest itself in an inoculated individual, it will be milder in character and the prognosis will be much more hopeful than in the case of an un-inoculated person.

This vaccine may also appropriately and safely be employed—in similar or even larger doses—for the treatment of healthy “carriers” of the meningococcus, after the first week of their infection.

MICROCOCCUS MELITENSIS VACCINE.

This vaccine is prepared from cultures of *Micrococcus Melitensis* obtained from the blood of cases of Malta Fever (Mediterranean or Undulant Fever) and is issued for use in connexion with that disease.

The small number of cases treated by vaccine up to the present does not warrant any confident statement as to the results which may be expected, but a definitely favourable impression has been registered.

The same consideration must be held to proscribe, for the present, the issue of precise recommendations with regard to dosage. It may be said, however, that treatment should be conducted in accordance with the general principles embodied in section 4, page 15, and that the minimum effective dose, appropriate to the stage of septicæmia with high fever, should be sought somewhat cautiously among doses up to 30 millions of cocci, while for the milder manifestations, muscular pains, etc., which are wont to recur during convalescence, relatively larger doses will be found requisite.

Occasionally, subsequent to the acute stage of Malta Fever, well recognisable periodic attacks of malaise occur. These attacks tend to continue over many months, and are very insidious in their onset. There is little or no fever, but marked malaise, with possibly some muscular pains, but the most marked feature is the subjective one of feeling “out of sorts.” Further, tests made during this period show that the agglutinative power of the serum is constantly fluctuating.

In this condition vaccine is of the greatest service; whilst the attacks tend to be regularly periodic, fortnightly doses are indicated; but when the attacks tend to be irregular in the onset, and occur at infrequent intervals, the vaccine should be held ready to be used as soon as an attack is recognised.

Doses of from 30 to 100 millions are indicated, and it has been found that a dose which produces malaise, or an increase of malaise, for 12 to 24 hours is an appropriate one.

The vaccine is issued in a dilution containing 100 millions of cocci *per c.c.* Minimum effective dose, 10 millions.

INTESTINAL INFECTIONS.

Intestinal infections, apart from the acute specific fevers, fall into two groups, streptococcal and bacillary.

The bacillary infections may be caused by one or other of the common intestinal inhabitants, or by the members of the food poisoning group of bacilli.

Intestinal Streptococcus Infections.

Definite streptococcal infections of the intestinal mucous membranes occur in acute ulcerative colitis and in recurrent gastro-enteritis. There are, however, no symptoms differentiating these diseases due to streptococci from similar clinical entities caused by other varieties of bacteria, and before recourse to vaccine therapy in this class of case is taken, a bacteriological investigation would seem to be imperative. Only slight additional work would be involved in preparing a vaccine from the patients' own streptococci, and in the majority of cases this course would naturally be followed. But where there was strong presumption, or definite evidence, that the condition was a streptococcal one, and it was not practicable to get an autogenous vaccine, an excellent substitute would be the Intestinal Streptococcus Vaccine (*see* page 40). The initial dose would vary with the severity of the case. Where the constitutional condition was grave, such an initial dose as 1 million of the mixed streptococci might be given, and a similar or larger dose might be appropriate the following day. As the dose increased, the period between would be lengthened. Where the condition was more chronic, such doses of the mixture as 5, 7½, 10, 12½, etc., millions might be essayed at weekly intervals.

Experience shows that there is a tendency for streptococci to show increased activity in the intestine during and subsequent to the existence of any chronic intestinal infection. There is no evidence that this occurrence, which seems to be a direct sequel, always occurs, but it is certainly frequent. As, however, it would only become apparent as the result of actual bacteriological investigation an autogenous vaccine would usually fill the requirements, though the Intestinal Streptococcus Vaccine would be an ample substitute.

In the writer's experience many cases of "shell shock" have proved to be the subjects of a profound intestinal streptococcal infection, and the condition has yielded to autogenous vaccines of intestinal streptococci, generally of a type other than "*streptococcus faecalis*." Especially are the depression and apprehensions of the condition brought under control. Treatment has to be persisted with, and the doses of vaccine may have to be carried to a high level before cure is obtained.

The Intestinal Streptococcus Vaccine (*see* page 40) is admirably adapted for the requirements of these cases.

Another class of cases in which streptococci are showing pathogenic activity in the intestine are termed toxæmias rather than infections, in that the organisms do not to any extent invade the mucous membrane, or at least cause no definite lesions therein. Such conditions will frequently be associated with a general lowering of the resistance to streptococci, as in cases of rheumatism of chronic type.

In view of the activity of streptococci, possibly of diverse strains in other parts of the body, a mixed streptococcus vaccine fulfils the requirements admirably. Such a mixed vaccine of streptococci recovered from cases of rheumatism is available, and the dosage thereof is discussed under the heading of "Anti-Rheumatic Vaccine" (see page 38).

THE "FOOD POISONING" GROUP OF INFECTIONS.

Strictly speaking, any intestinal infection that gains admission to the intestine through the mouth is a food infection, but used in this strict sense, the term would include typhoid fever, which is not usually included in the group.

Like the bacillus of typhoid, the bacilli of the food poisoning group are non-lactose-fermenters. That is to say, they do not acidify, or form gas in, lactose-containing media. It is not customary to include all the bacilli of the non-lactose-fermenting type under the term, though the tendency is to bring more and more non-lactose-fermenting bacilli into the group. Thus, for some years such a bacillus as the *Bacillus* of Epidemic Jaundice was considered of doubtful pathogenicity, but a case of septicæmia, simulating typhoid, caused thereby, definitely established its potential pathogenicity, and it seems reasonable to include it in the food poisoning group. Another bacillus, prior to the war of rare occurrence in this country, the *B. asiaticus*, would at that date hardly have been included in the group, but of recent years it has become so commonly the cause of intestinal infections, that it also seems to merit a place in the group.

The group at present may be said to include :—

The paratyphoid bacilli.

Gaertner's bacillus.

B. aertrycke.

Morgan's dysentery bacillus.

Bacillus of epidemic jaundice.

B. asiaticus.

B. pseudo-asiaticus.

B. pyocyaneus.

The infections caused by this group of bacilli are usually associated with recurrent attacks of gastro-enteritis. The clinical history of the illness may frequently be traced back to an acute attack of gastro-enteritis, which, if not associated with an epidemic outbreak of "food-

poisoning," may have suggested the tentative diagnosis of typhoid fever, but as the fever did not persist for more than three or four days, the diagnosis was not confirmed.

Chronic colitis may, however, be the result of this group of infections, and again, a member of the group may be found in profusion in a routine examination of a stool, when the symptoms had not led to the expectation of such an infection.

No stock vaccines are available of these bacilli. The diagnosis of this class of infection is generally established by bacteriological examinations of intestinal content, and the isolation and classification of the bacilli involved entails such a degree of work that the slight additional work entailed in the preparation of an autogenous vaccine does not materially add to the undertaking.

Infections due to the Bacilli of the Coliform Group.

The chief coliform bacilli in the normal intestine fall into four groups, viz :—

- (1) *B. coli communis*.
- (2) *B. coli communior*.
- (3) *B. lactis aerogenes*.
- (4) *B. acidi lactici*.

These bacilli are usually found in any specimen of normal stool, but one or more may be absent, and indeed one variety may dominate the picture to the practical exclusion of the others. Such preponderance of one variety is often found in cases of mucous colitis, summer diarrhoea, etc. To some extent the marked preponderance of any one of these four varieties suggests that the bacillus has achieved a pathogenic relationship to its host. Further evidence of such pathogenicity may be gained by serum methods, which, if undertaken, entail such a degree of work with isolated and classified cultures that the preparation of a vaccine entails but inappreciable extra effort.

Without undertaking an investigation of such scope recourse may be had to a vaccine containing members of the four common intestinal coliform bacilli, indicated above.

The majority of cases of cystitis and bacilluria, as well as many cases of pyelitis, are caused by one of the four groups of intestinal bacilli enumerated above, and in default of expert bacteriological examination, such cases may well be treated empirically with a stock vaccine of coliform bacilli. Acute cases of cystitis and pyelitis may require a scale of dosage more gradual than that suitable for chronic intestinal infections, but in such cases frequency of micturition is usually a very sensitive guide to dosage. The rule may be suggested that any dose which does not cause increased micturition during the following night is submaximal.

Coliform infections occur in other situations. Thus the middle ear, the antra, and the bronchial mucous membrane may at times prove to be so infected.

Coliform septicæmias occur, and though apparently idiopathic, are probably usually the sequel of some infected viscus, such as the gall bladder. Gall bladder infections are usually coliform in nature.

Appendix abscesses usually contain the coliform bacilli of the adjacent intestine, though careful examination may show that one variety is in preponderance, generally associated with streptococci.

Coliform bacilli are occasionally found in the uterus in puerperal infections, again usually associated with streptococci.

The nature of the foregoing infections will, as a rule, only be apparent as the result of expert bacteriological examination, in consequence of which an autogenous vaccine will generally be available, but in the event of such a vaccine not being forthcoming, the use of a stock vaccine may be considered. If there be evidence that the infection is a coliform one, a coliform vaccine would naturally be indicated, but as has already been said, many of the above infections are complicated with streptococci, usually of intestinal origin, and in such cases a mixed vaccine of coliform bacilli and intestinal streptococci is indicated.

The requirements as to coliform bacilli are met by the

MIXED VACCINE FOR COLIFORM INFECTIONS.

This vaccine is prepared from a selection of coliform microbes obtained in each case—and this furnishes a guarantee for their pathogenicity—from a genito-urinary or peritoneal infection.

Four different types of coliform microbes are employed, the composition of *each* c.c. of the vaccine being as follows:—

<i>Bacillus coli communis</i>	...	...	...	...	...	100 millions
<i>Bacillus coli communior</i>	...	...	...	...	...	100 millions
<i>Bacillus lactis aerogenes</i>	...	...	...	...	...	40 millions
<i>Bacillus acidi lactici</i>	...	...	...	...	...	20 millions

The vaccine is issued for the treatment of those cases of coliform infection where it is impracticable to prepare an autogenous vaccine. The cases—and it is chiefly cases of urinary infection which here come under consideration—may for the purpose of vaccine treatment be divided into cases of (1) chronic bacilluria without pyrexia or marked anæmia, and (2) bacilluric cases with either pyrexia or marked anæmia. In the latter class of cases it is essential to employ throughout only very small doses.

McCarrison has reported (*vide* Milroy lectures, *Lancet*, 1913, vol. i.) good results in cases of goitre treated with a similar mixed coli vaccine. These results have been confirmed by other observers.

In the less severe cases we may, while beginning with the minimum effective dose, gradually advance until we have found a dose which produces a slight amount of constitutional disturbance. It will then be advisable to give a dose somewhat less than this, repeating this dose

every week or ten days, and not advancing beyond it until we find that it is losing its effect. The same principle applies to the treatment of the cases of colitis which are associated with coliform infections.

Dosage.—The minimum effective dose will be about 0.1 c.c. The medium dose in an ordinary case is, approximately, 0.5 c.c.

ANTI-TYPHOID VACCINE.

Prophylactic Inoculation against Typhoid and Paratyphoid Fevers.

Sir Almroth Wright, who introduced this vaccine, showed that following the inoculation of dead typhoid bacilli in man the blood acquired to a marked degree the power of destroying the typhoid bacilli. After being used in small outbreaks in India and elsewhere, it was first employed on a large scale during the South African War. The results obtained during this campaign (although they showed a twofold decrease in the incidence of the disease and a fourfold diminution in the case mortality) were obscured by the incompleteness of the records and by the fact that in those days typhoid fever was not differentiated from the paratyphoid infections. This confusion led to a delay in the adoption of the prophylactic use of typhoid vaccine in the British Army, and it was not till 1909 that it was possible to convince the army authorities, both medical and military, that typhoid inoculation was a safe and useful procedure.

Prior to the great war, a series of reports from the Indian Medical Service had shown that the vaccine was of extreme value in preventing the disease, and that if the disease was contracted by an inoculated person it ran a much milder course and the case mortality was very much reduced.

In the early part of the great war the vaccine used was one of typhoid bacilli alone, but in February of 1916 it was decided to incorporate in the vaccine the paratyphoid bacilli A and B, and after that in the Army the mixed vaccine was given. This is known as the T.A.B. vaccine (*which see*).

As is well known, the amount of typhoid in the army in France was almost a negligible quantity, and was in very striking contrast to what had obtained in all previous campaigns. It was in striking contrast, also, to the results in all the other armies engaged on the Western Front in 1914 and 1915. In all these other armies there were considerable epidemics in the earlier months of the war and it was only after inoculation was practised as a compulsory measure in these armies that those epidemics ceased.

The figures for the British Army have been published by Sir William Leishman in the Medical History of the War, and a few extracts from these may here be set out as illustrating the effect of the vaccine.

The first table shows a comparison between the incidence and mortality from the Enteric Fevers in the South African War and in the Great War.

TABLE I.

The Relative Incidence and Mortality from the Enteric Fevers among the British troops engaged respectively in the South African War and in the war of 1914-18.

	Total cases.	Total deaths.	Case mortality.	Mean average strength.	Annual incidence per 1,000 of strength.	Annual death rate per 1,000 of strength.
South African War, 1899-1902	57,684	8,022	13.9	208,226	105.00	14.6
The Great War, 1914-1918	20,139	1,191	5.9	2,000,000	2.35	0.139

In this table no effort is made to differentiate typhoid from the paratyphoid fevers, and the figures here given relate to cases diagnosed as "Enteric Group" on clinical signs alone. These figures include the returns from all the zones in which the army operated and not only on the Western Front. The figures are so striking that they call for no comment.

The next table—Table II.—shows the mortality from typhoid fever during the first months of the war. At this time all the men were not inoculated. In the original Expeditionary Force only some 30 per cent. had received the vaccine, but the number inoculated had steadily risen till it was about 80 per cent. in January of 1915. This table shows that there is a very marked diminution in the case mortality in the inoculated men. Sir William Leishman comments on this table as follows: "Precise information on the inoculated strength was not possible to collect for military reasons, so that the incidence per thousand is not here given as in some of the other tables. All the same, the contrast in the case mortality is dramatic, as is the fact that only one death from typhoid occurred in this period in an inoculated man."

TABLE II.*

Total cases and case mortality from Typhoid Fever, B.E.F., Aug. 1914 to Jan. 29th, 1915.

	Cases.	Mortality.	Case Mortality.
Not inoculated within 2 years	305	34	11.1
Inoculated 1 dose T.V. within 1 year	83	1	1.2
Inoculated 2 doses T.V. within 3 years	33	—	—

Table III. shows the monthly rates of incidence of typhoid fever during 1915, and it will be seen from this that during each month

* In this and the subsequent tables the figures refer only to the British Expeditionary Force in France, as it was only here that laboratory and other facilities were available to a sufficient extent to render the findings trustworthy.

there was an enormous difference in favour of the inoculated man. For the whole year the total case incidence was 9.5 per 10,000 in the inoculated as against 103.52 in the uninoculated.

TABLE III.

Monthly rates of incidence of Typhoid Fever among the inoculated and non-inoculated during 1915.

	Percentage Inoculated.	Cases per 10,000.	
		Inoculated.	Non-inoculated.
January	80	2.98	9.93
February	88.3	1.85	17.76
March	92	1.41	21.33
April	93	0.8	8.59
May	94	1.1	8.46
June	95	1.84	2.74
July	95.8	1.0	2.57
August	97.1	0.89	4.51
September	97.5	0.49	4.1
October	97.5	0.41	1.72
November	98.1	0.23	2.27
December	98.5	0.23	5.53
For the Year	—	9.5	103.52

The year 1915 was chosen in this table as this was the first year in which military conditions permitted the compilation of the percentages of inoculated and uninoculated with accuracy. In the later years the number of uninoculated (during the whole war, inoculation remained voluntary) was so small that comparative figures were useless.

Table IV. shows the incidence of all the enteric group of diseases in the inoculated and the uninoculated during 1915. From this table it will be seen that even if all the diseases of this group had really been typhoid instead of being (as most of them were shown to be by definite bacteriological methods) infections quite distinct from that by the bacillus typhosus, there would yet have been a five-fold reduction of the case incidence among the inoculated.

TABLE IV.

Annual rates of the incidence of Typhoid, Paratyphoid and Enteric Group among the inoculated (with typhoid vaccine) and the uninoculated for 1915.

	Rate per 10,000.			
	1 Typhoid.	2 Paratyphoid Fever.	3 Enteric Group.	1+2+3
Inoculated, 614,715	9.5	21.53	2.87	33.91
Uninoculated, 29,365	103.52	39.84	7.49	150.85

It is not necessary to give further figures to illustrate the protection conferred by typhoid vaccine. Its value before the war was proved beyond doubt to thinking persons, and now the results obtained in the Great War are such as to convince the unthinking.

Special Instructions with regard to the Preventive Inoculation of Anti-Typhoid Vaccine.

Anti-Typhoid Vaccine is issued in sets of two bulbs, which contain respectively 1,000 millions and 2,000 millions of bacilli *per c.c.* It is recommended that, in the case of the ordinary healthy adult, 1,000 millions should be given for the first dose, and 2,000 millions should be given for the second, which should follow the first after an interval of ten days. Young children may receive 2 to 5 minims (0.1 to 0.3 c.c.), according to age, of the weaker vaccine for the first injection, and double that quantity ten days later. For convenience when several individuals have to be inoculated, a dilution containing 2,000 million bacilli *per c.c.* is supplied in bottles of 25 c.c., which provide sufficient vaccine for 16 double doses for adults, as mentioned above.

In the case of soldiers, it has been the practice to administer for the first dose 500 millions and for the second dose 1,000 millions of bacilli, the protection from which was expected to last during the period of the war. The larger doses are usually administered to civilians.

Owing to the fact that we are, in the case of Anti-Typhoid Vaccine, dealing with a toxic microbe, it is to be expected that after inoculation of a relatively large dose of that vaccine some amount of constitutional disturbance and of inflammatory reaction at the site of inoculation will ensue. Usually within a few hours, a rise of body temperature to 100° or 101° will occur, and be accompanied by some feeling of malaise, occasionally also by a slight rigor and nausea, but these symptoms, as also the local inflammatory tenderness, need occasion no alarm or call for any treatment, and may be confidently expected to abate within 24 hours.

With a view to minimising the constitutional disturbance, and in particular the tendency to faintness which may supervene where the patient exerts himself immediately after the inoculation, it is recommended that the inoculation shall be carried out in the late afternoon or early evening, and that the patient should be instructed to go to bed, in particular after the first inoculation, as soon as he feels any malaise. It is advisable, but not necessary, that the patient should remain in bed during the next forenoon. The discomfort arising from inflammatory reaction at the site of inoculation will also be minimised if the inoculation be made into a part of the body where the subcutaneous tissues are somewhat lax.

It is strongly recommended that no alcoholic stimulants be taken for 24 hours before, and 48 hours after, the injection.

TYPHOID VACCINE (for use in the Treatment of Typhoid Fever).

Within the last few years the treatment of this disease by means of vaccine has attracted considerable attention.

In the *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris*, Séance 18, Juillet, 1913, Netter summarises the published

reports of no less than 40 different authors with respect to 1,300 cases of typhoid fever thus treated, and finds that all but 4 of these authors are satisfied of the advantage accruing from the use of Typhoid Vaccine.

The most striking and significant of these reports is that of Petrowitch of Uskub, which treats of 460 cases inoculated with vaccine during the fever (usually 1 to 3 doses of 30 millions each), and of 220 uninoculated cases in the same hospital. Excluding from both series the cases which died within 24 hours of admission to hospital, the mortality among the inoculated cases was 2.24 per cent., as compared with 12.8 per cent. for the uninoculated.

A reduction also in the incidence of relapses and complications among cases treated with vaccine has been experienced by many authors.

There is no reason to suppose that an autogenous vaccine will give better results than the stock typhoid vaccine in this connexion.

Typhoid Vaccine is issued in a dilution containing 100 millions of bacilli *per c.c.*, for use in the treatment of typhoid fever.

Dosage.—Minimum effective dose, 20 to 30 millions; medium doses, 40 to 100 millions.

ANTI-PARATYPHOID VACCINE.

This vaccine is made from an equal admixture of *Bacillus paratyphosus A* and *Bacillus paratyphosus B*.

It has been recommended by certain authorities (Dreyer and Castellani) that this vaccine should be used in addition to Anti-Typhoid Vaccine so that immunity might be acquired to paratyphoid as well as to typhoid infections.

The vaccine is sent out in a strength suitable for prophylactic inoculations, but the vaccine can also be used for curative purposes in cases of paratyphoid infections. For curative purposes it ought to be diluted ten-fold with sterile water or salt solution, so that the required dose may form a convenient bulk.

The vaccine is sent out in 25 c.c. bottles containing 1,000 millions of each bacillus *per c.c.*, and in sets of two bulbs containing 500 millions and 1,000 millions, respectively, of each bacillus.

Dosage.—For prophylactic use, a first dose of 500 millions of each bacillus should be given, and followed in ten days by a dose of 1,000 millions of each.

For curative purposes it is well to commence with 10 millions of each bacillus, and to double the dose every five days provided there is no general reaction.

ANTI-TYPHOID-PARATYPHOID VACCINE (T.A.B.).

This vaccine is intended for use in those cases in which it is desired to administer a mixed prophylactic vaccine. This vaccine has largely supplanted Anti-Typhoid Vaccine, and is of the same formula as that which was used in the Army during the late war (*British Medical*

Journal, 1915, I., 758, and II., 610). When unspecified orders are received for prophylactic vaccine against typhoid or enteric fever, T.A.B. vaccine is always supplied.

The vaccine is sent out in 25 c.c. bottles containing in *each c.c.*: 1,000 millions of *Bacillus typhosus*, 500 millions of *Bacillus paratyphosus* (*A*) and 500 millions of *Bacillus paratyphosus* (*B*). Also in sets of two bulbs, the one containing 500 millions of *B. typhosus*, and 250 millions of both *A* and *B B. paratyphosus per c.c.*, labelled "first dose"; the other containing 1,000 millions of *B. typhosus* and 500 millions of both *A* and *B B. paratyphosus per c.c.*, labelled "second dose."

Dosage.—For the first dose 500 millions of *B. typhosus* and 250 millions of both *A* and *B B. paratyphosus*, that is, 0.5 c.c. of the vaccine contained in the bottles, or 1 c.c. of the contents of the bulb labelled "first dose," should be injected; from eight to ten days afterwards a second dose of 1,000 millions of *B. typhosus* and 500 millions of both *A* and *B B. paratyphosus*, that is, 1 c.c. of the vaccine contained in the bottles, or 1 c.c. of the contents of the bulb labelled "second dose," should be given. Similar symptoms to those occurring after inoculation with Anti-Typhoid Vaccine are to be expected, it is therefore recommended that the precautions given under the heading, "Special instructions with regard to the preventive inoculation of Anti-Typhoid Vaccine" (see page 69) should be taken.

ANTI-TYPHOID-PARATYPHOID-CHOLERA VACCINE (T.A.B.C.).

This consists of a mixture of these three vaccines, and is for use when it is desired to administer these together, as in cases where individuals are proceeding to infected districts and there is no time to administer the vaccines separately.

The vaccine is sent out in 25 c.c. bottles containing in *each c.c.* 1,000 millions of *B. typhosus*, 500 millions of both *A* and *B B. paratyphosus*, and 2,000 millions of cholera vibrios. Also in sets of two bulbs, the one, labelled "first dose," containing in *each c.c.* 500 millions of *B. typhosus*, 250 millions of both *A* and *B B. paratyphosus*, and 1,000 millions of cholera vibrios; the other, labelled "second dose," containing in *each c.c.* 1,000 millions of *B. typhosus*, 500 millions of both *A* and *B B. paratyphosus*, and 2,000 millions of cholera vibrios.

Dosage.—The first dose should be 0.5 c.c. of the vaccine in the bottles, or 1 c.c. of the vaccine contained in the bulb labelled "first dose"; the second dose, which should be given after an interval of eight or ten days, should be 1 c.c. of the vaccine in the bottles, or 1 c.c. of the vaccine contained in the bulb labelled "second dose." Rather more reaction is to be expected after the administration of such a mixed vaccine than when the vaccines are given separately, and the precautions recommended under the heading "Special instructions with regard to the preventive inoculation of Anti-Typhoid Vaccine" (see page 69) should be followed.

DYSENTERY BACILLUS VACCINE.

This vaccine is prepared from *B. dysenteriae* (Flexner), each c.c. containing 500 million bacilli. In a report on an epidemic of acute bacillary dysentery published in the *Arch. Med. Belg.* (Jan., 1921) it was stated that of 170 men attacked 75 showed Flexner's bacilli, and in cases where vaccine was administered almost all the patients became convalescent after three or four injections. The reactions following injection were very rare and slight.

In consequence of the prevalence of dysentery in mental hospitals, 126 persons having died out of 728 attacked during the second half of 1921, a recommendation was issued by the Board of Control that this vaccine should be used in cases of asylum dysentery, and some of the medical superintendents have done so with more or less satisfactory results. A mixed vaccine prepared from the Flexner and Shiga bacilli was suggested, but expert opinion inclined to the belief that the Shiga vaccine, if of any potency, is very toxic, while if so weak as not to be toxic it was likely to be of no value. The first vaccine supplied contained 50 millions per c.c., but experience led to the view that 500 millions of Flexner's bacilli of various strains per c.c. was a better strength, and this dilution is now supplied.

Dosage.—0.1 c.c., gradually increased to 1 c.c., may be given at intervals of four days.

CHOLERA.

This disease is caused by the *Vibrio cholerae*, the bacteria being confined almost strictly to the intestine. This is one of the first of human diseases in which vaccines were used for prophylactic purposes, and at first living cultures were used for injection. Now, however, dead cultures are used and the vaccines are prepared in exactly the same way as are the other vaccines such as typhoid, etc. It has been shown that the injection of cholera vaccine in man results in the production of bactericidal substances capable of destroying the cholera vibrio, and clinically it has been shown that by the administration of the vaccine the incidence of the disease is very materially reduced and also that the disease, if contracted, runs a less severe course.

ANTI-CHOLERA VACCINE.

This vaccine is made from strains of the cholera vibrio. To eliminate any small differences there may be between different strains of the microbe there has been incorporated in the vaccine a large number of strains of the cholera vibrio, thus rendering the vaccine an extremely polyvalent one. This makes the vaccine very valuable for the protection of persons who are proceeding to districts where cholera is likely to be met with.

The vaccine is sent out in 25 c.c. bottles, containing 2,000 million vibrios *per c.c.*, and in sets of two bulbs containing 1,000 millions and 2,000 millions, respectively.

Dosage.—Two doses are necessary—the first of 1,000 millions, followed after an interval of ten days by a dose of 2,000 millions.

This vaccine gives practically no reaction.

(For Anti-Typhoid-Paratyphoid-Cholera Vaccine (T.A.B.C.), *see* page 71.)

ANTI-PLAGUE VACCINE.

This vaccine is prepared from cultures of *Bacillus pestis*, and is issued as a prophylactic vaccine against plague.

In India, especially, anti-plague vaccines have been used for many years, and the results show definitely that they have considerable value as prophylactic agents.

The vaccine is issued in 25 c.c. bottles, containing 2,000 million bacilli *per c.c.*, and in sets of two bulbs containing 1,000 millions and 2,000 millions, respectively.

Dosage.—Two doses are necessary for prophylaxis, the first being 1,000 millions and the second 2,000 millions. The interval between the doses should be ten days.

THE PROTEIN IDIOPATHIES.

Treatment by Stock Vaccines of Asthmas, Food Poisonings, Urticarias, Angioneurotic Edema, Hay Fever, Horse Asthma, Migraine Headaches, Epilepsy, Eczema, etc.

In this section of our vaccine therapy booklet, where for the last twelve years the immunological treatment of hay fever has been described, it is now time to add a number of similar ailments of which a list (which is not exhaustive) appears above. These ailments are allied because they are, or may be, the result of a peculiar sensitiveness on the part of the sufferer to some foreign protein. This is a truism with regard to hay fever or horse asthma, generally admitted of most asthmas (bronchial asthma, for example), while for the others there is a strong case for saying that they are sometimes, if not always, so caused. It is not claimed, therefore, that we have a "cure" for all of them in the use of a stock vaccine; but such treatment is at least worth consideration.

Before setting forth the various vaccines and their uses some general observations must be made.

A. The protein, or proteins, afflicting a given patient may be of any kind derived from any foreign animal or vegetable substance. They may, *e.g.*, be products of some bacterium infecting the sufferer; be constituents of the food or drink he has swallowed; or be in the dust or clothing which comes in contact with his tissues parenterally.

The idiopathic action of these proteins is sharply specific. For example, there is a demonstrable difference between the action of the yolk and the white of an egg; of a hen's egg or a duck's egg; and between a fried, a lightly boiled, and an uncooked egg. Thus there is a wide choice of proteins, and for specific treatment it is necessary to know, or at least to guess, what the particular idiopathic proteins are likely to be.

B. *Diagnostic reactions* indicating the causal proteins can sometimes be usefully made—sometimes they cannot. In suspected cases the crude protein may be rubbed into the skin in a manner similar to the hay fever cutaneo-reaction (*see* page 78); for example, a suspected case of egg sensitiveness can be tested for with a drop of raw white of egg rubbed in with the end of a wooden match. For systematic protein testing, the series of Diagnostic Protein Extracts prepared by Parke, Davis & Co. may be employed. A list of upwards of 160 of these extracts will be found on a later page.

The investigator should, however, be warned on several points.

(1) Such a testing can never be complete, because the proteins are so specific and so numerous as to destroy all hope of a complete list.

(2) Protein-sensitive persons are frequently sensitive to a number of proteins; if so, the first half-dozen positive reactions may none of them indicate the chief factor in the patient's trouble.

(3) Positive reactions, when obtained, vary greatly in intensity. The pollen reactions of hay fever are more intense than those for animal asthmas; these latter are far more intense than the reactions produced by the food proteins; and these others, again, are far more intense than the slight reactions, if any, produced by bacterial and mould proteins. Thus the protein which is causing the trouble may give little or no skin reaction, but some other protein, though causing no symptoms, may give a relatively big reaction. This renders the situation the more difficult, because it is precisely the bacterial vaccines which are found in practice to be most frequently needed.

C. *The personal equation* is of quite a different order from that met with in straightforward bacterial infection. We are all more or less affected by the staphylococcus as an infecting agent, and therefore, it is a question of degree; but grass pollen, while it does not affect the normal man, will with a small percentage of persons always produce hay fever. So it is with the other proteins, including the bacterial; in a few people with the specific sensitiveness they will produce asthma, angio-neurotic oedema, eczema, etc.

D. *The sensitiveness* is a taint of which we do not understand the nature. It is clearly an abnormal condition, and is often compared to, or even identified with, anaphylaxis; there are, however, fundamental differences which we need not detail here. The taint shows marked heredity in its incidence, and a tainted family may show amongst its members a great diversity of protein sensitiveness; also any one member may suffer from several taints at once or at different periods of life.

E. "*Summation*" results from simultaneous protein sensitivenesses in one patient. Since they tend to produce very much the same syndrome, two or more proteins acting together will add their effects one to another. Successful treatment for one such protein will subtract from, but may not cure, all the symptoms. It is important to keep this point in mind both in diagnosis and treatment; an apparent failure of treatment often results from grasping only a part of the protein story.

F. *Trauma* plays some part in determining the form in which a protein sensitiveness shall express itself—e.g., as asthma, or urticaria, migraine, etc. Bronchial asthma follows bronchitis partly, no doubt, because the bacterial irritant is produced locally, but partly also because of the damage done by the infection. When once such damage has occurred and asthma has been established, then other protein irritants which may have gained access to the general circulation (food poisoning, for example) are also likely to express themselves as asthma. In the same way, angio-neurotic oedema is likely to occur at points of constant irritation—where the corsets rub the hips or where actinic rays of the sun strike the skin. Epilepsy, closely associated with other toxic idiopathies, may only commence after head injury, and migraine headaches with well-marked protein causes so often follow eye-strain as to justify treatment by correcting the eyesight with glasses.

G. *Nerve Reactions*. Nervous disturbances, such as emotion, profoundly affect the idiopathic syndrome. The disease is therefore peculiarly susceptible to suggestion, but this nervous factor is outside the province of vaccine therapy. Arising from these general observations we would suggest that four things are necessary to produce a protein idiopathy: (1) the taint of "sensitiveness" in the patient (see paragraphs C and D above); (2) the protein which corresponds with that taint (see paragraph A above); (3) some trauma or local disadvantage which determines the point at which the protein shall show its reaction, and (4) the nerve reaction which sets going the syndrome. It is the protein, or cause, which comes within the scope of vaccine therapy; the other three factors must be borne in mind either in making diagnosis or in judging the results of treatment.

DIAGNOSIS, PROPHYLAXIS AND TREATMENT OF HAY FEVER.**"POLLACCINE" (POLLEN VACCINE).****DIAGNOSIS OF HAY FEVER.**

Hay fever is the poisoning produced by the pollen of any grass or grain when it comes in contact with the mucous membrane of susceptible individuals. The pollens of all the grasses contain the same toxin, and any immunity acquired against one is acquired against them all. The toxin is present in the different grasses in very different concentrations. Grass pollen containing the greatest amount of toxin is that of timothy grass (*phleum pratense*), and it is therefore from this pollen that the extract has been made both for "Pollaccine" and for the diagnostic ophthalmo-reaction. These extracts are polyvalent to all hay fever. We state advisedly that no extra "polyvalency" can be achieved by adding pollens of other grasses and grains, or pollen of garden or meadow plants.

Hay fever can be diagnosed by:—

- (1) Its characteristic symptoms ;
- (2) Its periodicity, occurring when grass is in flower, and not at other times ; and
- (3) By a specific ophthalmo-reaction or cutaneo-reaction described below. This test can be made at any season of the year ; for instance, a case reporting in December can be tested then and there, and the diagnosis at once settled.

In using "Pollaccine" all three diagnostic methods are important. No. 1, because this will put the doctor and patient on the right lines ; No. 2, because if a *true* case of hay fever (*i.e.*, as shown by the specific reactions) begins much before mid-May or ends much after mid-July then some other complicating sensitization is to be suspected (see "Summation" in the preceding general observations) ; No. 3, because it is useless to immunize against pollen unless pollen is actually causing the symptoms from which the patient is suffering.

Rationale of the specific reactions. The offending protein, *i.e.*, grass pollen in this particular instance, will produce inflammation, oedema, etc., whenever and wherever it comes into contact with the living cells of the susceptible person. The conjunctival sac is a point where such a reaction can readily be observed—hence the ophthalmo-reaction. Any portion of the epidermis will also serve if the dead outer layer of skin cells are removed by scratching—hence the cutaneo-reaction. The technique here described ensures that the patient shall suffer only the slightest and most transient irritation.

The strength of the extract which is sufficient to produce the reaction is used as a guide to the dose, as is described later.

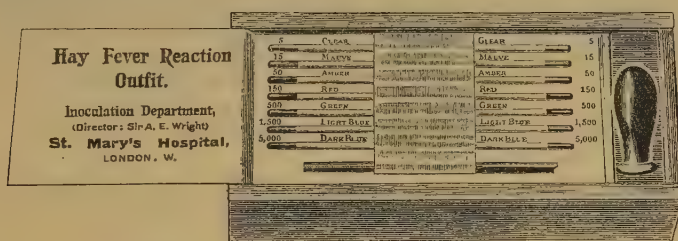
Materials Supplied for the Specific Hay Fever Reactions.

(1) Dilutions of pollen toxin* contained in capillary glass tubes distinguished by various colours:—

Clear tubes	...	...	...	...	5-unit strength
Mauve tubes	...	...	...	...	15-unit strength
Amber tubes	...	...	...	...	50-unit strength
Red tubes	...	...	...	...	150-unit strength
Green tubes	...	...	...	...	500-unit strength
Light blue tubes	...	...	...	...	1,500-unit strength
Dark blue tubes	...	...	...	...	5,000-unit strength

(2) A file with which to cut off the sealed ends of the capillary tubes

(3) A rubber teat, the closed end of which has been pierced so that a pin-hole is formed which will firmly hold a capillary tube when passed through it.



Graduated dilutions of pollen toxin for testing by the ophthalmo- or cutaneous reaction the degree of susceptibility in any hay fever subject, by which test the dose of 'Pollaccine' appropriate to the individual may be ascertained.

Method of Carrying out the Hay Fever Ophthalmo-Reaction.—This reaction in the case of a susceptible individual consists only of a slight and transient conjunctival or nasal irritation, quite unlike the rather serious consequences of the tuberculin reaction of Calmette. Place the patient in a chair facing a good light (daylight, if possible) and note whether there is normally an equal redness of the conjunctiva and caruncle of the two eyes. From the Hay Fever Reaction Outfit take one of the weaker strengths of extract—in a very severe case the capillary tube with clear glass ends which contains the weakest pollen extract (5-unit strength). Pass one end of this through the pin-hole in the rubber teat, and continue to push it through until the end of the tube emerges beyond the open end of the teat. With the file remove this end of the tube, and then withdraw until only about half an inch is contained in the body of the teat. Next cut off the other end, taking care to keep the tube horizontal. It is important in cutting off the two ends of the tube that the cut should be made cleanly, no splinters of glass being allowed to remain.

The next step is to drop the contents of the tube on to one of the eyeballs of the patient. To do this, direct the patient to throw his head back and look upwards. Take the teat loosely between the

* Pollen toxin is the active ingredient in "Pollaccine," but the latter is not suitable for the ophthalmo-reaction owing to its containing 0.5 per cent. of carbolic acid as a preservative.

thumb and first two fingers, then point the tube downwards towards, but be careful not to touch, the patient's eye. Pressure between the thumb and index finger will now close the mouth of the teat, and further pressure between the second finger and thumb will compress the air contained in the body of the teat, and will thus blow the contents of the tube on to the eyeball.

The patient may now bring his head forward to a more comfortable position, and at the end of a few minutes the eye should be examined for signs of reaction.

The first sign is usually a tickling sensation at the inner canthus of the eye, and this is accompanied, or shortly followed, by a slight but definite reddening of the caruncle and its neighbourhood. This is easily detected when the two eyes are compared. If this reaction is obtained the test is complete ; but if after waiting for three minutes no reaction has occurred, the next strength of the pollen toxin should be dropped on to the other eye, and the effect observed. If still no reaction occurs, continue the test with successively stronger solutions, alternating the eyes, until either a reaction occurs or all the test solutions have been used.

It should be noted that the very faintest reddening of the eye constitutes a reaction. If the reddening is at all marked, let us say with the amber tube (50-unit strength), then in this case the mauve tube (15-unit strength) would have just produced it. And if the reaction is *very* marked with the amber tube, then it is probable that the clear tube (5-unit strength) would have produced it.

If the patient gives this reaction with any of the solutions supplied, he is a hay fever patient and the extract which just produces a reaction indicates the relative susceptibility of the patient and so the dose to be employed. The normal individual never gives this reaction with any strength of extract or even with the crude pollen.

Method of carrying out Hay Fever Cutaneo-Reaction.—The cutaneo-reaction is hardly capable of producing unpleasant symptoms however roughly it is carried out ; indeed in very slight cases of hay fever even the crude grass pollen may be rubbed on to the skin for a "yes-or-no" diagnosis (see paragraph B, page 74). It is better, however, to test quantitatively because it is useful to know the degree of sensitiveness of the patient when gauging the dosage.

Instead of dropping the extract of grass pollen into the conjunctival sac, drop it on to any scratched surface of the epidermis. The forearm is convenient for men, and just above the knee for women and children. The object of the scratching is to remove the dead horny layers of the skin from the living tissues beneath ; as in small-pox vaccination, it should just fail to draw blood. Reactions appear in about 15 minutes and take the form of an urticarial wheal surrounded by an erythematous blush. The strength necessary to produce a minimal reaction is 3 to 10 times that necessary for the eye reaction, from which the correct dosage may be calculated.

PREVENTION AND TREATMENT OF HAY FEVER.

(A). **Prophylactic or Preventive Inoculation given during the Winter and Spring.**
(For Therapeutic Dosage during the actual onset of hay fever, see page 82).

The Ophthalmic- and Cutaneo-Reactions as a Guide to Dosage.—Not only does a reaction give a specific diagnosis, but the strength of the extract which just produces it will be a guide to the suitable dose for inoculation.

The Amount of each Prophylactic Dose.—The correct prophylactic dose is one-third of the number of units strength which just produced the ophthalmic-reaction, or one-tenth of the unit strength which produces a well-marked cutaneo-reaction. Apparently no useful object is served in exceeding this dose; a dose of more than 500 units is not recommended, and if one of the larger doses is selected as appropriate for a mild case it is safer to work up to it by the inoculation of one or two smaller doses.

If for any reason it is decided to try inoculation treatment without the help of ophthalmic-reactions, then the only guidance is the average reaction of hay fever patients during the winter. For this average see the second column of the following table of prophylactic doses.

TABLE OF PROPHYLACTIC DOSES.

(a) Strength of the Oph- thalgo- Reaction.	(b) Percentage of cases in which this reaction is likely to occur.	(c) Amount of dose of 'Pollaccine' to be inoculated.	(d) Quantities of "Pollaccine" which will give the doses indicated.			
			if the 5 units per c.c. 'Pollaccine' is used.	if the 20 units per c.c. 'Pollaccine' is used.	if the 100 units per c.c. 'Pollaccine' is used.	if the 500 units per c.c. 'Pollaccine' is used.
5 units strength	in 2% of cases	2 units	0.4 c.c. (7 minims)	0.1 c.c. (2 minims)		
15 units strength	in 4% of cases	5 units	1 c.c. (17 minims)	0.25 c.c. (4½ minims)	0.05 c.c. (1 minim)	
50 units strength	in 19% of cases	15 units	—	0.75 c.c. (14 minims)	0.15 c.c. (3 minims)	
150 units strength	in 45% of cases	50 units	—	—	0.5 c.c. (9 minims)	0.1 c.c. (2 minims)
500 units strength	in 22% of cases	150 units	—	—	1.5 c.c. (25 minims)	0.3 c.c. (5½ minims)
1,500 units strength	in 8% of cases	500 units	—	—	—	1 c.c. (17 minims)
5,000 units strength	(rarely occurs)		—	—	—	

The above table of prophylactic doses gives (a) the strength of pollen extract necessary to produce the ophthalmic-reaction, (b) the percentage of cases in which these ophthalmic-reactions are likely to occur, (c) the appropriate dose for the treatment of these cases,

(d) the volume of "Pollaccine" which must be inoculated in order to give this dose. It will be noted that in prophylactic inoculation from 50 to 100 units *per c.c.* "Pollaccine" will be most frequently of service.

The Time and Frequency of Inoculating.—The doses should be given every week or ten days. It is recommended that in very severe cases they should be commenced in the early winter, the milder cases being allowed to commence treatment later in the winter or even in spring. While one can say with confidence that such a prolonged course of inoculation, given regularly, will almost certainly stop or profoundly modify the attacks of hay fever, it is clearly much more difficult to say what is the *minimum* of inoculation necessary to bring relief. No doubt there is here a large personal factor.

The prophylactic doses should be continued till the height of the summer, but should there be an attack of hay fever they must be cut down and treatment continued with therapeutic doses (*see next page*) whilst the symptoms persist.

After-effects.—There is usually no after-effect, though there may be slight local reaction at the site of inoculation, and no constitutional disturbance after a dose. The only serious discomfort to be apprehended is an attack of urticaria. Should this occur, it can be cut short by one or two doses of calcium lactate, grs. 30. If the patient gives an emphatic history of nettlerash it is well to give this dose of calcium lactate at the time of inoculating, and again a few hours later. If an attack of urticaria takes place at all, it is usually only in connexion with the first dose of "Pollaccine."

The above suggested course of prophylactic inoculation has been on its trial now for 14 years and on the whole has answered well. Every year, so far as can be ascertained, about 75 per cent. of cases so treated, and some of these were really desperate, have responded well; the remaining 25 per cent. of cases have received only partial or negligible relief. Some of these failures or partial failures are accounted for by the complications produced by other protein sensitizations (*see* paragraph E on "Summation" in the preceding general remarks, page 75). However, an alternative method of prophylaxis is suggested below which has not yet had such an extended trial but which has given good results in the past two years; it is a system which, in certain circumstances at any rate, may be preferable to the older method.

(B). Intensive Prophylaxis against Hay Fever (a Course alternative to that described above): to be given in late Spring.

(Therapeutic dosage during the actual hay fever is described later.)

Those who have inoculated against hay fever know that, either through ignorance or because the memory of the mid-summer trouble has grown dim during the winter, patients have a way of coming to the doctor too late for the full course of prophylaxis sketched above. This full course was arranged as if hay fever inoculations were similar

to inoculation against a bacterial infection ; it is really more like the "desensitizing" with horse dandruff vaccine in cases of horse asthma (described on page 85) which has proved successful. There is in fact no discoverable reason why hay fever and horse asthma should be treated differently ; further, this intensive course gives a considerable advantage in the time required, since a fortnight, or a little over, should be enough. A "safe" initial dose is given—probably somewhere between 10 and 100 units in strength ; it is as well to judge of this from the specific ophthalmo- or cutaneo-reaction. The doses are repeated every day or every other day according to circumstances, and are increased by 50 per cent. to 100 per cent. each time if this is not contra-indicated. If there is a reaction from any dose this will take place within a few hours and may take the form of headache, urticaria, slight asthma, or general malaise : should this occur, the succeeding dose must either be the same or smaller according to the intensity of the reaction, and thereafter the increase in dose should be conducted more gradually. In this way it is recommended that the dose should reach 500 or 1,000 units and then be stopped ; but a "sticking point" beyond which the dose cannot be increased without symptoms may be reached before a 500 unit dose can be attained. In any event it should be the object of the inoculator to conclude the treatment within a few days of the expected commencement of the hay fever.

THERAPEUTIC TREATMENT AFTER THE ONSET OF HAY FEVER SYMPTOMS.

(For Preventive Treatment during the winter and spring see page 79 and page 80.)

Cutaneo- or Ophthalmo-Reaction as a Guide to Dosage.—As is the case with prophylactic inoculations, the reaction not only gives the diagnosis but also assists in fixing the dose. However, it is less necessary to use the reactions when one is inoculating *therapeutically* during the summer season : this is so for three reasons. (1) When the patient is, or has recently been, suffering from hay fever, the practitioner has clinical evidence for making his diagnosis, and therefore has the less need of a specific reaction. (2) When actually suffering from hay fever, the patient's eyes tend to be very sensitive, and if the ophthalmo-reaction is carried out rather too vigorously the eye may remain sore for a considerable time. This does not apply to the cutaneo-reaction. (3) The practitioner can regulate the size of the dose and the frequency by the clinical results, precisely as he regulates the inoculations with any other vaccine.

When inoculating with "Pollaccine" in the hay fever season we have to face the same difficulties as when inoculating against a bacterial infection therapeutically as opposed to prophylaxis ; it is impossible to lay down a fixed optimum dose. The amount of pollen which has recently collected on the mucous membranes of the patient, or which will collect in the near future, complicates our problem ; one can estimate

this from the state of the weather or from hearing what the patient has recently been doing and proposes to do. The other main factor is the sensitiveness of the patient to grass pollen ; this can be ascertained by the specific reactions previously described (*pages 77-8*), or assumed from the history of the patient. A reasonable therapeutic dose may be taken as one-tenth the number of units which just provoked the ophthalmo-reaction, but this estimate takes no account of pollen from the atmosphere at the moment and in the near future. If the practitioner decides to omit the specific reactions the following table of average therapeutic doses may help him to reach the same figures. It has been compiled from a large number of actual cases in the same way as the table on page 79.

TABLE OF THERAPEUTIC DOSES.

(a) Test dilutions causing Ophthalmo- Reaction.	(b) How often this reaction is to be expected.	(c) Appropriate dose of "Pollaccine" to be inoculated.	(d) Amounts of "Pollaccine" to be inoculated.		
			when using the 5 units per c.c. "Pollaccine."	when using the 20 units per c.c. "Pollaccine."	when using the 100 units per c.c. "Pollaccine."
5 units	8% of cases	$\frac{1}{2}$ unit	0.1 c.c. ($\frac{1}{4}$ minims)	0.025 c.c. ($\frac{1}{4}$ minim)	
15 units	19% of cases	$1\frac{1}{2}$ units	0.3 c.c. (5 minims)	0.1 c.c. ($1\frac{1}{2}$ minims)	
50 units	44% of cases	5 units	1 c.c. (17 minims)	0.25 c.c. ($4\frac{1}{2}$ minims)	
150 units	21% of cases	15 units	3 c.c. (50 minims)	0.75 c.c. (14 minims)	0.15 c.c. (3 minims)
500 units	7% of cases	50 units	—	2.5 c.c. (42 minims)	0.5 c.c. (9 minims)
1,500 units	1% of cases				
5,000 units	(very rarely occurs)				

The above will indicate the order of dosage likely to be found of benefit, but, broadly speaking, the inoculator must administer the doses according to the hay fever symptoms : if these are very acute he must give small doses (5 to 10 units) and repeat them frequently ; if the symptoms are less intense or grow less under treatment the inoculations can with advantage be larger and be given at longer intervals ; but in no case is a dose much larger than 50 units recommended. If any of these doses, including the "small" initial ones, provoke anything of a reaction or increase of symptoms the succeeding doses must be cut down below the reaction point. If there is doubt, as there well may be, as to a reaction having occurred, it is perhaps best to continue with the same dose until the practitioner has made up his mind.

Frequency of Inoculation.—It is necessary to avoid producing a negative phase which would be signalized by a violent attack of hay fever. It is for this reason that the minimum effective dose should be aimed at (*see section 5, page 18*) ; thus the effects are transient

and the dose must be quickly repeated—in the case of the larger dose, after a week ; and in the case of the smaller doses, after even a shorter interval. It is impossible with this comparatively small therapeutic dose to build up a large amount of immunity ; the best that can be done is to enable the patient to tide over the immediate future.

The results are sometimes so successful that patients will declare that they wish for nothing better, but with the majority the preventive treatment in the winter or spring is more effective and more to be recommended.

It sometimes happens that unpleasant symptoms follow too large a dose of "Pollaccine." Should these occur they can be controlled by the immediate injection, hypodermically, of 5 minims of Solution of Adrenalin Chloride, P., D. & Co.

DURATION OF ACTIVITY OF "POLLACCINE."

Both for the "Pollaccine" and for the reaction sets the pollen extracts are made from the preceding June pollen crop collected from a specially planted farm. This extract gradually diminishes in strength, but nevertheless it remains potent for very many years ; for example, the first extract made in the autumn of 1909 will still function as antigen and give a strong diagnostic skin reaction, though it has necessarily dwindled somewhat in strength during all these years. However, it can be assumed that the extracts may be used both for diagnosis and for treatment for two years at least after they have been collected, without the slightly diminished potency in any way complicating the calculations.

"Pollaccine" is issued in five dilutions, containing, respectively, 5, 20, 100, 500 and 1,000 units of pollen toxin *per c.c.*, the last-named being supplied in 1 c.c. ampoules only for the intensive prophylactic treatment described above. The physician is again warned that this or any of the larger doses should only be given after preliminary inoculations with smaller doses.

HORSE ASTHMA.

This is a counterpart of hay fever. In both conditions the symptoms are caused by sensitiveness to a foreign protein ; the protein is carried in fine particles in the air ; and, therefore, it is in the eyes, nose, and throat that it comes most quickly and intimately into contact with the living tissues of the victims. As might be expected, the syndromes are similar if not identical. In the one case it is the pollen of the grasses and grains which causes the trouble, in the other case it is the dandruff from the coats of horses. If allowance is made for this difference of protein irritant all that has been said under the heading of hay fever is true of horse asthma.

It can be diagnosed in the same three ways.

- (1) Its symptom complex, which is similar to that of hay-fever.
- (2) It occurs only when some horse substance comes in contact with the tissues.
- (3) A diagnostic reaction can be constructed by deliberately bringing horse dandruff into contact with the living cells.

Of these methods the first should be regarded as an indication of an air-borne protein irritant. The second is naturally important as indicating the particular irritant, and usually it is the first thing the patient will mention; the practitioner must bear in mind, however, that horse-flesh, material from horse-hair upholstery (including mattresses), horse serum (in serum therapy), horse-dung (an inevitable component of road dust in dry weather), or the presence of someone who has been with horses (*e.g.*, wearing riding breeches), may not occur to the patient. If symptoms also occur when no horse substance is present, the possibility of some other protein irritant must be considered: for example, many horse asthmatics have either hay fever or bronchial asthma, or both (see general observations, sections "D" and "E"). The third method of diagnosis is fortunately reliable and easy to carry out.

Rationale of the Cutaneo-Reaction (as the practitioner will probably be testing with an unmeasured strength of protein it is preferable not to employ the ophthalmo-reaction).

Horse dandruff is the most frequent and most potent form of this irritant, therefore both the diagnostic agent and the antigen are made from it. Of the various preparations on the market the most convenient are the Diagnostic Protein Extracts made by Parke, Davis & Co., referred to in detail subsequently. However, a hair or two freshly plucked from any horse will give as strong a reaction as an extract; the only danger is that in a very sensitive case it may be a little too potent. Should Protein Extract or material from a horse not be at hand it may be well worth while to use one of the three strongest ampoules contained in the set of "Hippaxine" for desensitization; that is, an ampoule containing 50,000 units of horse dandruff in a cubic centimetre of fluid. The reaction is precisely similar to that of grass pollen for hay fever (*q.v.*). Make two scratchings through the skin of a convenient site, on one scratching put water or any neutral substance, and on the other rub the horse hair protein extract, horse hairs, horse dandruff, or whatever horse preparation may be to hand. In a positive reaction the horse substance will bring up a patch of œdema surrounded by erythema in 15 minutes which will fade away in another 15 minutes; nothing will happen on the control. The normal (*i.e.*, non-horse-asthma) patient will never show such a reaction.

A still more sensitive reaction is obtained by dropping the fifth strength of extract of Horse Dandruff into the conjunctival sac; but this eye reaction should certainly not be employed until the skin test has failed, because it might be so severe as to be distinctly inconvenient to the patient for an hour or so. Again, let us insist that such a

reaction, while quite reliable as to horse asthma, does not necessarily reveal the *whole* of the protein story.

Treatment.

Desensitization of horse asthma patients is fairly simple and straightforward, but it makes considerable demands on both the patient and practitioner. The patient must be prepared to put himself in the doctor's hands for a fortnight or three weeks; not to stay in bed, but to have daily treatment and to be under daily observation. The practitioner has to adapt the course of inoculation to the particular needs of each individual patient. Persistent disregard of reactions in the patient after dosage, or a serious mistake in the quantity of "Hippaxine" given by the doctor, would produce phenomena sufficiently unpleasant to make the patient terminate treatment there and then if he is at all nervous. Should unpleasant symptoms arise they will be only temporary, and can be cut short at once by a subcutaneous injection of Adrenalin, 1 : 1000 solution, say 0.3 c.c. (5 minims), which the doctor may be presumed to have by him, seeing he is dealing with an asthmatic case; however, this will not be needed if the instructions sent out with each set of doses of "Hippaxine" are followed.

Complications by other Protein Sensitizations.

Beyond warning the patient that he should not approach this business in too casual a spirit, there are one or two medical points to be considered before deciding to embark on a course of desensitization.

There is the certainty of diagnosis; this will have presented no difficulty with an intelligent patient possessing well-marked symptoms, but patients sometimes exaggerate and may be mistaken.

A second medical point is the possibility that though horse sensitization is present it may not be the main causal factor in the production of the symptoms—asthmatic, or whatever they may be; it is common to find a number of different protein sensitizations in one patient. If some other protein or proteins are giving rise to more symptoms than are derived from the true horse asthma, then even complete desensitization with "Hippaxine" may disappoint the patient. As against this it may be asserted that if two or more factors are operating together, let us say some bronchial asthma and some asthma derived from horses, removal of either one or the other factor will lessen the total symptoms. To put the matter shortly, if two or more protein factors have been detected, or are suspected, the physician must assure himself that the horse asthma factor is the one best worth attacking before he resorts to the use of this vaccine.

During treatment, all horse substances (other than the vaccine) should, if possible, be kept from the patient—both for his own sake and to avoid confusion; this will reduce the problem of immunization from one of therapeusis to one of prophylaxis. Even so, no two cases will be alike. We may estimate that about two weeks will be necessary for the treatment, which is similar to the "intensive" prophylactic treatment for hay fever described above (page 80).

The ampoules containing the "Hippaxine" are put up in five different strengths designed to give a range of dosage from 8 units to 50,000 units; a "set" contains three ampoules of each strength. If during the treatment more than three ampoules of any one particular strength are needed, extra supplies can be obtained separately. The set is as follows:

3 ampoules of	No. 1 strength	(80 units "Hippaxine" per c.c.)	
3 "	" No. 2	(400 "	)
3 "	" No. 3	(2,000 "	)
3 "	" No. 4	(10,000 "	)
3 "	" No. 5	(50,000 "	)

Commencing with a safe subcutaneous dose, progressively increasing amounts should be given every day, or every other day, as may be practicable. The "safe" dose depends on the severity of the case, and may vary from, say, 8 or 10 units for a high degree of sensitiveness, up to perhaps 80 units for a slight case. An average initial dose will thus be about 40 units of "Hippaxine," which will be obtained by taking half a cubic centimetre, or $8\frac{1}{2}$ minims, of the No. 1 strength. (Here it may be pointed out that the record of the series of doses given to a patient should be kept in terms of units of the antigen, and not by fractions of a cubic centimetre or by the number of minims.)

If, as is probable, there is no reaction whatever from the first dose, 80 units may be injected on the next day; the 80 units can be obtained by injecting either the full cubic centimetre from the weakest strength or a fifth of a cubic centimetre (roughly $3\frac{1}{2}$ minims) from the second strength supplied. If there is still no suggestion of any reaction, a third dose of, say, 160 units can be administered by taking two-fifths of a cubic centimetre from the second strength of ampoules, and so on.

By "reaction" nothing so gross as a rise in temperature is contemplated; urticaria, malaise, headache, irritability, or any asthmatic tightness across the chest, occurring within an hour of the dose, should suggest the possibility of a reaction; though this might be mere coincidence. If a reaction is suspected, it is better to give the same dose on the succeeding day; if the reaction is undoubted, and severe, it is better to give a smaller dose. In this way, increasing at first by 100 per cent. daily, later on by perhaps 50 per cent., or even less if there have been reactions, the dose can be steadily increased, but the increase should be checked at once, directly there is the slightest reaction, then after two or three doses of the same strength it is usually possible to resume cautiously the increasing of the doses.

Frequently a case will not permit the inoculations to be increased up to the full 50,000 unit dose, the patient showing persistent reactions with something smaller than this. In that event, two or three doses of the highest strength that the circumstances permit should be given, and then the course of treatment should be concluded.

TREATMENT OF BRONCHIAL ASTHMA BY A STOCK VACCINE.

Presumably, bronchial asthma would be defined as asthma caused by bronchitis. The designation "bronchitis" might cover any chronic catarrhal infection of the air passages, since the symptoms of asthma will follow such an infection if the sufferer is sensitive to the proteins of the infecting organisms. One may find most distressing asthma symptoms accompanying a degree of infection so slight as to be otherwise quite insignificant. In this section of Vaccine Therapy it is with the *sensitiveness* and not with the actual *infection* that we are concerned; it is comparable to the sensitiveness of the hay fever sufferer to grass pollen, only in bronchial asthma the luckless individual has, so to speak, the infective agent growing in his throat.

The symptoms will give the general diagnosis of asthma. Unfortunately (*see general observations, section E, page 75*), the cutaneous reactions with the microbic substance are seldom reliable—though they may sometimes be obtained; it is chiefly on the time relation that the physician relies for making a diagnosis of bacterial sensitization. "First began after an attack of measles," or "got very much worse after an attack of influenza," are common histories. In general the attacks of asthma will synchronize with coughs and colds and with chronic bronchitis; they will therefore be worse in the winter, or may occur solely at that time.

It is important to realise that a correct diagnosis of *bronchial* asthma does not exclude other protein irritants: on the contrary it may almost be said to suggest them, so usual are multiple sensitizations. These may cause the symptoms of any protein idiopathy—hay fever, horse asthma, a food sensitization, etc.,—and when these other proteins are operating the asthma will get worse, but when they lessen or stop in their action the asthma part of "bronchial" asthma will tend to improve, or may even be insufficient to produce symptoms. The intermittent action of these other proteins will make it more difficult to judge of the effect of any treatment by clinical results, and they will add to the patient's distress; it is generally impossible to detect and deal with them all, but the removal of any one will help the patient. (*See general remarks, section E, page 75*).

There is another side to all this: when dealing with a case of asthma (or any other of the protein idiopathies) which one would declare was "caused" by some food protein, or some protein irritant floating in the atmosphere, or from a cause unknown (as is usual with the locality asthmas, for example), in such cases some bronchial asthma is a frequent accompaniment. (*See general observations, section F, page 75*.) Therefore, for symptoms apparently derived, for instance, from food, or from some quite undetected protein, the most practical treatment may well be by a catarrhal vaccine.

Efficient inoculation for bronchitis and catarrh of the air passages is discussed on page 41. If one could stop the bronchitis one would stop the bronchial asthma; usually, however, suitable doses for this would be much too strong for asthma. With smaller doses one may desensitize, thus removing the *asthma* symptoms, but leaving the infection; then with larger doses the catarrh itself may be treated. The doses for asthma—to commence with, at any rate—should be one-fifth to one-tenth the dose suitable for the infection. For this purpose a Mixed Vaccine for Bronchial Asthma is recommended. As with the prophylactic inoculation for hay fever it may be used in one of two ways.

(1) The doses may be given once to twice weekly, commencing with one-tenth or one-fifth of a cubic centimetre according to the severity of the symptoms, the dose being inversely proportioned to the asthma. If the initial doses seem too weak they may be cautiously increased, but should be decreased at once if a definite reaction is produced: in fact, they should be used as if for bronchitis but the dose should be smaller, as has been explained.

(2) The second or intensive method is to keep the patient in bed and re-inoculate every day or every second day, increasing by 100 per cent. to 50 per cent. if this is not contra-indicated by a reaction. If and when the dose reaches one cubic centimetre of the Mixed Vaccine for Bronchial Asthma the process may be continued with any of the catarrhal vaccines which the practitioner may select—preferably, perhaps, the “Mixed Vaccine for Colds.”

By “reaction” is signified the smallest noticeable result occurring within twenty-four hours, or at most forty-eight hours, after the dose; the practitioner is again warned on two points: (a) if he asks about the reactions too insistently they will probably be produced to order; (b) careful watch must be kept for the effect of other protein sensitizations acting intermittently and so producing apparent “reactions.”

A DILUTE STREPTOCOCCUS VACCINE FOR PROTEIN IDIOPATHIES.

A patient may be sensitive to chronic infective processes other than catarrhs, etc., of the air passages; and of these, infections of the bowel are the most important, but chronic infections of any site (e.g., of the uterus or prostate) may serve. It has been shown (Bronchial Asthma, page 47) that a protein sensitization by an infection of the air passages usually produces asthma as its most prominent symptom: sensitization from these other localities may produce asthma but has

a chance of producing some one of the other protein idiopathies. Catarrh of the bowel may, and usually does, produce local trouble which signalizes itself as nausea, vomiting, and diarrhœa—or, if slight, it may be spoken of as “indigestion.” But, from the bowel at any rate, there is such rapid absorption that conditions approximate to an intravenous injection of the protein and constitutional effects follow. When these manifest themselves the protein idiopathy produced will to some extent depend on damaged and congenitally weak points (see general observations, paragraph F, page 75). When another active protein irritant is present it is uncertain where this wandering irritant in the blood may elect to augment the symptoms. Thus may be produced urticaria, eczema, ichthyosis—“asthmas of the skin”; thus, again, angioneurotic cedema and intermittent hydrarthrosis; or, if in the eyes and nose, the symptoms may be described as “perennial hay fever”; lastly migraine, headaches or epilepsy may undoubtedly follow as reactions to protein sensitiveness. To cause a given protein idiopathy syndrome there are frequently several proteins operating either simultaneously or successively: the discovery of protein action other than bacterial (*e.g.*, sickness and urticaria after eating egg, or eczema after eating wheaten bread) does not rule out the possibility of a streptococcal catarrh of the bowel assisting the phenomena—quite the reverse in fact. Bowel sepsis is the commonest and most potent cause, and a streptococcal catarrh would appear to be the most common form of such bowel sepsis. That is the justification for the streptococcus vaccine treatment which is now advocated, but if the trouble is from an infection other than streptococcus the help of a bacteriologist is required.

Before deciding to use the weak streptococcal vaccine it will be seen that two questions may very properly be asked: (1) Is the condition one of protein idiopathy at all? (2) Is streptococcus likely to be the chief, or at any rate a considerable, protein factor? As to the first question, note the generalizations briefly summarized on pages 74-5. The physician, however, will tread firmer ground if he finds that other protein idiopathies are, or have been, suffered by the patient or by his blood relatives: *e.g.*, it would be reassuring to our diagnosis to find that the brothers and sisters of a migraine sufferer have hay fever and that a parent had had asthma.

On the second question he gets confirmatory evidence if his patient has a “streptococcal history” (and skin, teeth, throat, bowel, uterus, etc., may all contribute to this), *e.g.*, have there been threatenings of appendicitis or colitis? Above all, do the exacerbations of the protein idiopathy synchronise with this streptococcal story?

The use of the vaccine.—As with hay fever, horse asthma, etc., the Intestinal Streptococcus Vaccine may be used in one of two ways.

(1) A minimal dose is used, always keeping to something less than will produce any noticeable reaction or malaise in the patient. Half a million will be a convenient initial dose and this is given in one-fourth of a cubic centimetre of the weakest *Intestinal Streptococcus Vaccine*. With such small doses re-inoculations may be given twice weekly if practicable, and in the absence of reaction the dose may be cautiously increased, to be reduced however, and kept reduced, on obtaining any definite reaction. Somewhere between one and two millions (*i.e.*, between 0.5 and 1 cubic centimetre of our vaccine) will frequently be found to be the operative dose. It may be said of this method that it is very safe and it frequently gives very good results. It is, however, long; and it demands assiduity and enthusiasm on the part of the patient and practitioner.

(2) An intensive course. Since such a course may be successfully used in hay fever and horse asthma (and has been described under those headings: page 80) it is logical to consider it with streptococcal proteins also. A safe initial dose will be half a million or even less of the *Intestinal Streptococcus Vaccine*, and the dose should be rapidly augmented at daily or two-daily re-inoculations. The increases may at first be by 100%, later on by, say, 50%, and when reactions seem to be threatening even a smaller increase should be given. Any definite reaction such as malaise or increase of the protein idiopathy in question should make the practitioner repeat the same dose, or even give a diminished dose. When, as will quickly happen, the full cubic centimetre of the weakest vaccine is being given, the course may be continued with the stronger concentrations, such as the anti-rheumatic streptococcus vaccine.

THE DANGER OF OVER-DOSAGE.

In view of the repeated requests for highly concentrated vaccines it seems essential to repeat that, save in exceptional cases such as when a definite protein reaction is called for, large doses of vaccine ought never to be employed in treatment. The general rule should be adhered to, that the more acute the infection the smaller should be the dose. We therefore repeat the warning given on page 25 that doses in treatment should be inversely as the volume of the patient's operative infection, and when the optimum dose is reached it ought not to be exceeded without very careful consideration. There is reason to believe that much harm may be done by giving massive doses of vaccine in therapeutic treatment, and it is probable that such doses as are sometimes advocated are free from positive danger only because of the harmlessness of vaccines prepared by unscientific methods.

SCHEDULE OF VACCINES.

All of these vaccines are sent out in 1 c.c. ampoules and also, in many cases, in 25 c.c. rubber-capped bottles.

Vaccines marked thus (†) are sent on unspecified orders.

Acne Bacillus Vaccine.

In dilutions containing, respectively, 20† and 500 millions of acne bacillus *per c.c.*

Mixed Vaccines for Acne.

†MIXED ACNE VACCINE, "A", containing 1,000 millions of staphylococcus albus and 20 millions of acne bacillus *per c.c.*

MIXED ACNE VACCINE, "B", containing 1,000 millions of staphylococcus albus and 500 millions of acne bacillus *per c.c.*

Actinomycosis Vaccine.

In a dilution containing 25 millions of mycelial fragments *per c.c.*

Anti-Catarrh Vaccine.

Containing in *each c.c.* 50 millions of bacillus pneumoniae (Friedländer), 250 millions of pneumococcus, 50 millions of micrococcus catarrhalis, 50 millions of bacillus septus (diphtheroid), 250 millions of bacillus influenzae, and 25 millions of streptococcus.

Also see Mixed Vaccine for Colds and Mixed Anti-Influenza Vaccines.

Anti-Cholera Vaccine.

Sets of two immunising doses, respectively 1,000 and 2,000 millions of vibrios.

Anti-Meningococcus Vaccine.

Dilution containing 1,000 millions of diplococcus intracellularis meningitidis *per c.c.*

Anti-Paratyphoid Vaccine.

Sets of two immunising doses, respectively 500 and 1,000 millions of paratyphoid bacilli (A and B).

Anti-Plague Vaccine.

Sets of two immunising doses, respectively 1,000 and 2,000 millions of B. pestis.

Anti-Rheumatic Vaccine.

In dilutions containing in *each c.c.* respectively 5, 20, 50†, 250 and 500 millions of streptococci isolated from the mouth, intestine and genito-urinary tract of patients suffering from rheumatism or rheumatoid arthritis.

Antisepsis Vaccine (Mixed Staphylococcus and Streptococcus).

Containing in *each c.c.*: 1,000 millions of staphylococcus, 20 millions of streptococcus pyogenes and 30 millions of other types of streptococci isolated from septic wounds.

Anti-Typhoid Vaccine.

Sets of two immunising doses, respectively 1,000 and 2,000 millions of typhoid bacilli.

Also see Typhoid Vaccine.

†Anti-Typhoid-Paratyphoid Vaccine (T.A.B.).

Sets of two immunising doses, the first containing 500 millions of *B. typhosus*, 250 millions of *B. paratyphosus* A, and 250 millions of *B. paratyphosus* B, and the second containing twice these numbers of the respective bacilli.

Anti-Typhoid-Paratyphoid-Cholera Vaccine (T.A.B.C.).

Sets of two immunising doses, the first containing 500 millions of *B. typhosus*, 250 millions of *B. paratyphosus* A, 250 millions of *B. paratyphosus* B, and 1,000 millions of *V. cholerae*, and the second containing twice these numbers of the respective bacilli.

Asthma Vaccine. *See* "Hippaxine" (Horse Dandruff Vaccine) and Mixed Vaccine for Bronchial Asthma.

Coliform Vaccine. *See* Mixed Vaccine for Coliform Infections.

Dysentery Bacillus Vaccine.

Containing in *each c.c.* 500 millions *B. dysenteriae* (Flexner).

Gonococcus Vaccine.

In dilutions containing, respectively, 5, 20, 50†, 200 and 500 millions of gonococci *per c.c.*

Mixed Gonorrhœa Vaccine.

Containing in *each c.c.*: 500 millions gonococcus, 1,000 millions staphylococcus, 100 millions streptococcus, 200 millions diphtheroid bacillus.

Hay Fever Vaccine. *See* "Pollaccine."

"Hippaxine" (Horse Dandruff Vaccine).

In dilutions containing, respectively, 80, 400, 2,000, 10,000, 50,000 units *per c.c.* Supplied in sets of 15 ampoules.

Influenza Bacillus Vaccine.

In dilutions containing, respectively, 100, 500† and 1,000 millions of bacilli *per c.c.*

Mixed Anti-Influenza Vaccines.**†ST. MARY'S HOSPITAL FORMULA.**

Containing in *one c.c.*: *B. influenzae* (Pfeiffer), 500 millions; pneumococcus, 1,000 millions; streptococcus, 100 millions.

ARMY FORMULA (ORIGINAL).

Containing in *one c.c.*: *B. influenzae* (Pfeiffer), 60 millions; pneumococcus, 200 millions; streptococcus, 80 millions.

Intestinal Streptococcus Vaccine.

In dilutions containing, respectively, 2, 10, 50 and 500 millions of streptococci *per c.c.*

Micrococcus Melitensis Vaccine.

Containing 100 millions of cocci *per c.c.*

Mixed Vaccine for Bronchial Asthma.

This vaccine is one-fifth the strength of the Mixed Vaccine for Colds.

Mixed Vaccine for Colds and other Respiratory Catarrhs.

Containing in *each c.c.*: 25 millions micrococcus catarrhalis, 50 millions pneumococcus, 50 millions bacillus influenzae, 200 millions staphylococcus, 25 millions bacillus septus (diphtheroid), 10 millions streptococcus, and 25 millions bacillus pneumoniae.

Also see Anti-Catarrh Vaccine.

Mixed Vaccine for Coliform Infections.

Containing in *each c.c.*: B. coli communis, 100 millions; B. coli communior, 100 millions; B. lactis aerogenes, 40 millions; B. acidi lactici, 20 millions.

Parodontal Streptococcus Vaccine.

Containing in *each c.c.* 30 millions of streptococci.

Pneumococcus Vaccine.

In dilutions containing, respectively, 20, 50† and 200 millions of pneumococci *per c.c.*

Also see Mixed Vaccine for Colds.

"Pollaccine" (Pollen Vaccine for Hay Fever).

In dilutions containing, respectively, 5, 20, 100†, 500 and 1,000 units of pollen toxin *per c.c.*

Hay Fever Reaction Outfit.

Containing seven capillary tubes of pollen toxin in graduated dilutions (5, 15, 50, 150, 500, 1,500, and 5,000 units), with apparatus for instilling the toxin into the patient's eye for the ophthalmic diagnosis of hay fever.

Capillary Tubes of Pollen Toxin for the Diagnostic Test.

The several strengths of pollen toxin contained in the Hay Fever Reaction Outfit are supplied in packages of 2 and 12 capillary tubes.

Staphylococcus Vaccine.

In dilutions containing, respectively, 100, 500† and 1,000 millions of staphylococci *per c.c.*

Also see Mixed Vaccine for Acne and Antisepsis Vaccine.

Streptococcus Pyogenes Vaccine (Polyvalent).

In dilutions containing, respectively, 5, 20† and 100 millions of streptococci *per c.c.*

Also see Antisepsis Vaccine, Intestinal Streptococcus Vaccine and Parodontal Streptococcus Vaccine.

Tubercle Vaccine (Tuberculin: Bacillary Emulsion).

In dilutions containing, respectively, *per c.c.*, the quantities specified of powdered tubercle culture :

*1/100,000	milligram	(0.00001 mgm.)
1/40,000	"	(0.000025 ")
1/25,000	"	(0.00004 ")
*1/10,000	"	(0.0001 ")
1/5,000	"	(0.0002 ")
1/2,000	"	(0.0005 ")
†*1/1,000	"	(0.001 ")
1/500	"	(0.002 ")
*1/100	"	(0.01 ")

Dilutions marked with an asterisk (*) are supplied in 25 c.c. bottles

Typhoid Vaccine for Use in the Treatment of Typhoid Fever.

Containing 100 millions of typhoid bacilli *per c.c.*

Also see Anti-Typhoid Vaccine.

Whooping Cough Vaccine.

(A) PROPHYLACTIC. Containing in *each c.c.* : 4,000 millions Bordet's bacillus.

(B) PROPHYLACTIC. Containing in *each c.c.* : 4,000 millions Bordet's bacillus, 500 millions influenza bacillus, 100 millions pneumococcus.

†(C) FOR TREATMENT. Containing in *each c.c.* : 500 millions Bordet's bacillus, 250 millions influenza bacillus, 20 millions pneumococcus.

HOW SUPPLIED

All the above vaccines are supplied in 1 c.c. ampoules, and in many cases also in 25 c.c. rubber-capped bottles.

Sets of 3 graduated doses of Anti-Catarrh Vaccine and Mixed Anti-Influenza Vaccine (S.M.H.) are supplied.

NOTE.—A dose of vaccine to represent any number of organisms other than the number contained in one of the 1 c.c. ampoules may be obtained by taking a proportionate quantity from an ampoule containing a higher number, or from a bottle of the vaccine. When less than 1 c.c. is withdrawn from an ampoule, the remainder may be preserved for future use if the neck of the ampoule be sealed with wax. The ampoule should be well shaken before the dose is withdrawn.

PART II.

SERUM THERAPY.

Serum therapy is a considerably older department of medicine than vaccine therapy, and though the younger system has a somewhat similar sphere and a much wider scope, the older has still its own particular field which may be defined as the production of passive immunity, whereas inoculation with a vaccine gives rise to active immunity. It may not be amiss briefly to outline the difference in the constitution and mode of action of the two classes of antibacterial remedies.

Active Immunity.

Bacterial vaccines consist of suspensions of pathogenic bacteria that have been counted and sterilised without undue heat. When injected into the patient's tissues the bacteria are digested and certain substances—antigens—are set free; these stimulate the formation of antibodies capable of counteracting infection; that is to say, the vaccine confers *active* immunity. The process usually requires several days for completion and during the early portion of that period the patient's disease-resisting powers are slightly reduced (negative phase) before the increase (positive phase) sets in, but the immunity produced is more enduring than that following passive immunisation.

Passive Immunity.

Immune serums contain antibodies developed in the blood of an animal in response to inoculation with gradually increased amounts of a toxin or bacterial culture. When a dose larger than would ordinarily be lethal can be injected without causing any constitutional disturbance, or in other words, when the animal has become immune, a quantity of the blood is drawn off and the serum separated for therapeutic use.

When this serum is injected into a patient suffering from the infection to which the animal supplying the serum has been immunised, it provides ready-formed substances capable of antagonising the infecting organisms, that is to say, it confers *passive* immunity, without making any demand on the patient's own disease-resisting powers, therefore it does not set up any progressive therapeutic process, and the immunity lasts for a short time only. The effect, however, is prompt, and the occurrence of a cure usually depends upon the use of a sufficient quantity of the serum.

The outstanding indication for the use of such serums as can be produced is in acute forms of the respective infections, when there is no time to wait for the production of active immunity by vaccine therapy.

Antitoxic Serums.

Some types of bacteria produce in the media surrounding them (whether in the animal body or artificial culture media) poisonous substances which have been termed toxins. Diphtheria and tetanus bacilli are examples of these. The toxins produced can be demonstrated in the culture media after the organisms have been removed, their potency accurately estimated and their activity determined by tests on animals. In order to render possible recovery from an infectious disease such as diphtheria, a substance must be formed somewhere in the body which will either render the toxin inert or counteract its destructive action. This neutralising substance, the presence of which can be demonstrated and its specific energy measured, is known as antibody (antitoxin). This same antitoxin can be produced in a similar way by injecting into an animal toxin produced artificially in culture medium; the antibody can later be demonstrated in the serum of the animal. When this immune serum is injected into an individual suffering from the disease, its specific antibody augments the antibody that is being formed by the tissues as a defence against the infection, and the resulting protective alliance will, if the serum is given early enough and in sufficient quantity, overcome the disease.

The potency of antitoxic serums can be accurately determined by observing the quantity required to protect a guinea-pig from being harmed by the injection of a lethal dose of toxin.

Antibacterial Serums.

Certain other types of bacteria, such as the *Streptococcus* and *Gonococcus*, produce toxic substances which are intracellular in character and which are liberated only upon the destruction of the organisms in the animal body. They are therefore called endotoxins in contradistinction to the true toxins (exotoxins), such as those of diphtheria or tetanus, which are found as excretions in the filtered culture medium. This type of organism does not stimulate the body cells to produce an antitoxin, that is, a substance which neutralises the toxin alone, but it excites the cells to form other substances, demonstrable in the blood-serum, which act directly on the bacteria, causing them to become disintegrated. A serum containing this sort of antibody is called an antibacterial serum, and is produced by the injection of the bacteria, either dead or alive, into animals. In the preparation of serums of this class, the endeavour is made to obtain the highest possible content of antibodies, and they are tested in various ways to determine the strength as far as possible.

The Integrity of "P., D. & Co." Serums.

In no other department of medicine is there greater need for absolute reliability than in serum therapy. In many cases a life depends upon the integrity of the serum used.

Many years' experience in serum production, the possession of ample facilities and the collaboration of a corps of specially trained scientific workers place the laboratories of Parke, Davis & Company in a particularly favourable position for the supply of thoroughly trustworthy serums.

The firm commenced work of this character immediately after the International Congress of Hygiene at Budapest in October, 1894, when the reports of Roux, Behring and Aronson on diphtheria antitoxin were given to the world. When the Government of the United States enacted that serum production should only be carried on under official sanction, License No. 1, dated August 21, 1903, was issued to Parke, Davis & Co.

Since that time, so great has been the increase in the work of the firm's Biological Laboratories that it has been found necessary to acquire a farm of 700 acres at Rochester, about 30 miles from Detroit. Parkedale Farm is at an altitude of 600 feet above sea level, it is traversed by several streams of pure water, is well drained, and provides excellent pasturage for the large number of animals required in the work. Buildings for laboratory and administrative purposes are constructed on the most approved principles; a condition of asepsis is everywhere rigidly enforced; all surgical work is performed in buildings separate from those in which animals are housed, and newly-arrived animals are isolated for at least a week before being admitted, if they pass inspection, to the general stables. Parkedale Farm is under the immediate supervision of fully qualified medical men and veterinary surgeons, and associated with them is a staff of trained bacteriologists and other skilled workers.

The firm has never relaxed its efforts to improve, where possible, upon past achievements. Constant study has been directed towards the elucidation of many problems relating thereto—culture media, methods of producing toxin of highest potency, immunising procedures, reduction in volume of the dose and also in protein content of serum—in all these matters great improvements have been effected.

In addition to the testing of the antitoxin unit strength of such serums as admit of it, all serums are rigorously tested for purity and innocuity by bacteriological and physiological methods. Furthermore, in order that the profession may have a perfectly independent guarantee, "P., D. & Co." Antidiphtheria, Antitetanus and Antistreptococcus Serums destined for the European markets are submitted for examination in the Laboratory of the Inoculation Department at St. Mary's Hospital, London (Director: Sir Almroth Wright, M.D., etc.), whose certificate is attached to every bulb.

Keeping Properties of Serum.

A gradual loss of potency occurs in all antitoxic serums, to compensate for which there is included in each bulb of "P., D. & Co." serum sufficient excess to ensure, under normal conditions, the presence of the stated number of antitoxin units until the date indicated on each package.

In so far as antitetanus serum is concerned recent experience indicates that the effect of exposure to relatively high temperatures is not so detrimental as has sometimes been stated. A supply of Parke, Davis & Co.'s Antitetanus Serum, sold to a public department was shipped by the purchasers to East Africa *via* the Red Sea, without any precautions being taken as to storage on board ship, and the serum was in consequence exposed to the usual risks from high temperature. On being informed of what had happened Parke, Davis & Co. offered to test samples of the serum, and a number of bulbs were returned from East Africa for that purpose. The retest, which was carried out in 1924, showed that the potency had not fallen to any appreciable extent, the actual number of antitoxin units contained in the serum being in excess of the figures stated on the label.

Injecting Serum.

For administering serum the "Glaseptic" All-Glass Serum Syringes are strongly recommended. They consist of two parts only—barrel and piston—which are constructed of specially well annealed glass and are carefully ground to ensure a perfect fit. They are readily sterilised by boiling. They may be had separately or complete with two steel needles and a filling canula in a nickel-plated case, which is so constructed as to be adapted for use as a steriliser.

Injection into a muscle (for example, the vastus externus) secures quicker absorption than injection into subcutaneous tissue (e.g., under the skin of the abdomen, thigh, nates, the interscapular region, or side of the breast). In some cases, intravenous or intrathecal injection is called for. The skin at the point of injection should be washed with Germicidal Soap (P., D. & Co.) or with plain soap and water followed by 5% carbolic acid solution.

Injections for prophylaxis should be given subcutaneously; for treatment, by the intramuscular, intravenous or intrathecal route.

To fill the syringe, shake down into the body of the serum bulb any fluid that may be in the neck, make a notch round the neck with a file, place a finger and thumb above and below the notch and break off the tip. Using a sterilised syringe and needle, draw up the contents of the bulb into the syringe, then holding the latter with the needle pointing upward, expel all air from above the level of the serum. Inject slowly—the pain and shock are then much less than when a shorter time is taken over the process. If only part of the contents of a bulb of serum is injected, the remnant should be thrown away; it is not desirable to use it on a subsequent occasion.

Sequelæ.

Some hours or even days after an injection of serum erythema may appear, also slight local pains, numbness and, occasionally, pains in the joints. These are, as a rule, transitory, and need excite no alarm; small doses of sodium salicylate or aspirin are reported to hasten their subsidence. In order to prevent possible attacks of urticaria, or serum rash, 30 grains of calcium lactate may be given at the time of injection; and a similar dose a few hours later.

Anaphylaxis.

A writer in *The Lancet* of January 20, 1917 (p. 109), states that anaphylaxis is not likely to occur in patients who have previously had only small (prophylactic) doses of serum, but is more likely in those who have had massive doses six or more weeks previously. When anaphylaxis is feared, 0.5 c.c. of the serum should be given at first, followed by gradually increased amounts every 5 or 10 minutes until the required dose has been attained. In the same journal (p. 124) another writer states: "Anaphylactic symptoms coming on at once, and serum rashes coming on after an interval, are rapidly controlled by subcutaneous injections of Pituitrin. In anaphylaxis, 1 c.c. given at once, relieves the collapse and spasm of the bronchioles within a few minutes. The dose should be repeated if the symptoms show any sign of returning. A similar plan is equally successful in serum rashes." Such reactions may also be controlled by a hypodermic injection of 5 minims of Solution Adrenalin Chloride (P., D. & Co.).

ANTIDIPHTHERIA SERUM.

(Diphtheria Antitoxin)

This serum is obtained from horses that have been rendered immune to the toxin of the diphtheria bacillus by a series of gradually increased doses, commencing with a very small dose and augmenting progressively until, after a period of several months of such treatment, the horse is unaffected by the injection of massive quantities of the toxin.

The Chief Medical Officer of the Infectious Hospitals Service (London), writing in *The British Medical Journal* of June 9, 1923, refers to the large number of cases of diphtheria which are in a hopeless condition when admitted to hospital. He says: "In view of the almost invariable success of antitoxin if administered in the early stage of diphtheria, and the comparative harmlessness of the remedy even should its use subsequently prove to have been unnecessary, the record must be regarded as deplorable." He is convinced, he says, that "the most frequent source of delay in treatment is the fatal practice of awaiting the result of the bacteriological examination before deciding to give antitoxin or sending the case into hospital. Hesitancy to certify for removal before the diagnosis is confirmed is

not unnatural, but the same objection does not apply to giving antitoxin. Until practitioners can be persuaded to administer serum on the mere suspicion of a case being one of diphtheria, the sad experience of patients being so frequently sent into hospital in a hopeless condition will continue to be a reproach to the profession."

In severe cases of croup, and in all suspicious cases of tonsillitis, it is desirable to administer diphtheria antitoxin at once and forward a swab from the throat for bacteriological examination afterwards.

Antidiphtheria Serum is used prophylactically as well as in treatment. It may be administered intramuscularly or intravenously. In most cases the former will suffice, but when a prompt effect is essential, the intravenous method is to be preferred.

Dosage in Treatment.—It is advisable to administer 5,000 or 10,000 antitoxin units in all ordinary cases. If no improvement is manifested in 24 hours, it is then advisable to repeat the quantity first given. The physician must be guided by the apparent requirements of the case, and it should be borne in mind that a single dose of 20,000 units is much more effective than two doses of 10,000 units on successive days. As children are more susceptible to the disease than adults, and have far less power of resistance, they require at least as large a dose, if not larger.

A memorandum issued by the Ministry of Health (see *Brit. Med. Journal*, 1922, II, 484) enjoins that in every case where a provisional diagnosis has been made, at least 8,000 antitoxin units (whatever the age of the patient) shall be injected as early as possible without waiting for bacteriological confirmation of the diagnosis. Intramuscular injection is preferable to subcutaneous, as it secures quicker absorption. If the first dose is followed by definite improvement within about twelve hours, further serum may not be required, but if there is no improvement, or if the disease is plainly progressing, a second dose should be given, and repeated if no distinct improvement occurs.

Prophylactic Doses.—It is generally considered advisable to administer 1,000 units to each person who has been exposed to infection, particularly where such contacts cannot be kept under daily observation so that antitoxin might be given at short notice if symptoms should develop.

"P., D. & Co." Antidiphtheria Serum is supplied in two grades—X or Standard Grade and XX or Special Grade—which differ merely in the volume in which a given number of antitoxin units is presented. By using the "Special" grade, which contains from 1,400 to 1,500 units per c.c., the required number of units may be injected in a smaller volume of serum than if the "Standard" grade is given, and cutaneous eruptions are less likely to occur.

Each bulb contains the number of antitoxin units specified on its label, though the volume in which that number is presented may vary slightly from time to time according to the ascertained potency of the particular batch of serum.

Local Treatment must not be neglected. For this purpose Hydrogen Peroxide Solution (P., D. & Co.) or diluted Fecto (P., D. & Co.) may be applied to the throat several times daily by means of a swab or spray.

Constitutional Treatment.—No specific treatment other than the use of serum and topical remedies is indicated, but care should be taken that the eliminative organs are doing their duty. Some authorities recommend the administration of 5 minims of Adrenalin Chloride Solution, in water, every four hours, to support the heart. Pituitrin (P., D. & Co.) is of value for counteracting low blood pressure. For maintaining nutrition, milk predigested by means of Peptonising Tablets (P., D. & Co.) is of service, and for assisting convalescence Nucleo-Proteid Compound Tablets (P., D. & Co.) are useful.

ANTITETANUS SERUM

(Tetanus Antitoxin)

Antitetanus Serum is obtained from the blood of horses that have been hyperimmunised by the injection of gradually increased amounts of tetanus toxin. It is standardised by ascertaining the amount necessary to neutralise the minimum fatal dose of tetanus toxin when serum and toxin are simultaneously injected into a guinea-pig.

The volume in which any stated number of units is contained may vary, inasmuch as the concentration of the serum yielded by the horse varies from time to time, but the all-important feature is the number of antitetanus units present, and this is certified by the St. Mary's Hospital Inoculation Department on the label affixed to each bulb of P., D. & Co. serum.

Prophylactic Use.—The prevention of tetanus is a much simpler matter than its cure, and the prophylactic value of injections of Antitetanus Serum is beyond all question. It should be administered hypodermically immediately after any injury which may give rise to tetanus, *e.g.*, all wounds soiled with earth, street dirt or horse manure. The usual prophylactic dose is 1500 units, administered subcutaneously. At the same time the wound should be thoroughly cleansed with Hydrogen Peroxide Solution, and curetted or cauterised. In the case of extensive or heavily contaminated wounds the dose should be repeated once or twice at intervals of seven days.

In a Memorandum on Tetanus issued by the War Office Committee on the study of Tetanus, in 1916, it is stated that "the prophylactic

value of injections of Antitetanic Serum is beyond all question, but there is strong experimental evidence that in about ten days the immunity conferred by the primary injection is to a great extent lost."

Use in Treatment.—For curative effect the antitoxin must be injected at the first sign of the disease, for the tetanus toxin soon forms such a fixed combination with the nerve ganglia as to render futile later attempts at neutralisation with the antitoxin.

It is recommended that at least 20,000 units should be given, partly intravenously, to neutralise the toxin in the circulating blood and lymph, and partly intraspinally to combat the toxin that may be in the spinal cord and medulla. The intravenous injection should be repeated at least once after an interval of 24 hours, and the intraspinal injection should be repeated daily until signs of improvement appear, then the intervals may be lengthened and the dose reduced as the condition of the patient warrants.

The patient will be benefited by medication adapted to allay the reflex excitability of the cord, and for this purpose Chloretone is said to be safer and more effective than chloral or other drugs. It is administered by rectal injection—60 grains (3.8 gm.) of Chloretone dissolved or merely diffused in a suitable quantity of warm olive oil. Cases have been reported (*Journ. of Obstetrics*, June, 1909, p. 415; *Brit. Med. Journ.*, 1909, I., 1024, and 1910, II., 1402) which show the great value of supplementing the injection of Antitetanus Serum by a Chloretone and olive oil enema.

Some authorities (*The Lancet* of January 27, 1917, pp. 131-9) are not convinced of the necessity for intrathecal injections. They suggest that if the wound is a single one, especially if on a limb, antitoxin should be introduced both subcutaneously and intramuscularly somewhere astride the path which the toxin must travel on its way to the spinal cord, the dose to be divided and portions injected on each surface of the limb, and also at different depths amid the muscles. The more evenly it is distributed the greater is the probability that the antitoxin will encounter and neutralise the toxin.

ANTI-ANTHRAX SERUM.

Anthrax, otherwise termed charbon, milzbrand, or splenic fever, is an acute infectious disease of domestic animals, particularly cattle, sheep and horses, caused by the anthrax bacillus and characterised anatomically by an acute swelling of the spleen and by serous hæmorrhagic infiltrations of subcutaneous and subserous connective tissues.

Anthrax may also attack the human subject, and in this form it is known as "woolsorters' disease" or "malignant pustule." The

appearance of the pustule is very characteristic ; in the centre is a brownish, almost black, crust, and round this is a ring of small vesicles, which is in turn surrounded by a halo of dusky-red indurated skin.

Until recently no cure was known, but the use in veterinary medicine of a specific serum obtained from the blood of animals that have been immunised against several strains of *B. anthracis* has led to the remedy being employed in human practice.

The following report of a human case treated with Veterinary Anti-Anthrax Serum (P., D. & Co.) comes from M.B., B.S., Lond. " M., aged 48, bought a shaving brush on a Saturday and used it on Sunday morning. He sent for me on the following Wednesday stating that he thought he had influenza, and that his jaw was stiff and painful. He had a small and very characteristic pustule situated exactly in the middle of the chin, the glands under the chin being enlarged, hard and tender ; temperature 101°. Having seen several cases when a student at Guy's I recognised the condition. A film prepared from the exudate from the pustule and stained showed anthrax bacilli, and I immediately wired to Parke, Davis & Co. for serum. On the following morning I injected 30 c.c. which produced an immediate effect, and two days later a similar dose was given. The pustule had by that time almost dried up, the glands were soft and no longer tender, and the patient was quite well by the following Sunday. Anthrax spores were found in the shaving brush by the Ministry of Health bacteriologist, and other brushes in the same batch were also infected. I did not excise the pustule, thinking it would be useless to do so and leave infected glands." (January 5, 1922.)

Dosage.—The Ministry of Health circular of January 28, 1921, recommends the *intravenous* injection of 60 to 80 c.c. of anti-anthrax serum as soon as symptoms are recognised, and 60 c.c. on the day following if there is no improvement. The subcutaneous injection (into the abdominal wall) of 30 c.c. repeated, if necessary, on successive days, has been successful in some cases.

ANTIDYSENTERIC SERUM.

This serum is obtained from the blood of horses which have been immunised to polyvalent suspensions of *Bacillus dysenteriae* isolated from cases of dysentery, and including several strains of both the Shiga and Flexner types.

The use of this serum is indicated in all early cases of bacillary dysentery, such as epidemic jail and asylum dysentery, as well as in those cases of infantile summer diarrhoea which are due to infection with *B. dysenteriae*.

An investigation carried out at the instance of the Medical Research Council in 1916 on the nature of dysenteric infection in cases returned

to this country, showed that the Mediterranean epidemic of "dysentery" was highly complex in character. Both amœbic and bacillary infections existed side by side, or in the same individual. A number of so-called dysentery cases were really cases of paratyphoid A. and B. Serum tests showed that 31·3 per cent. of all the cases gave a positive agglutinating reaction with *B. dysenteriæ* (Shiga), and 11·1 per cent. with *B. dysenteriæ* (Flexner).

In the *Indian Medical Gazette* (1922, p. 85) it is reported that in the early stages of acute bacillary dysentery in Mesopotamia the stools gave cultures of Shiga and Flexner bacilli in nearly 60 per cent. of cases, and only in the early stage was serum effective.

One writer states (*Lancet*, 1919, II., 778) that in cases treated early by serum, the acute stage was shortened, the tendency to chronicity lessened, and convalescence rendered more satisfactory than in those treated later, either by serum or other methods. Serum sickness occurred in 56 per cent. of the cases. In fairly severe cases 140 c.c. of the serum were given, in three subcutaneous injections at 8 hour intervals: in less severe cases, 100 c.c. were given in two injections at 12 hour intervals.

In cases of summer epidemic diarrhœa in Melbourne, Flexner dysentery bacilli were found in two-thirds of the cases showing blood and mucus in the stools, and in one-third of those with only pus cells or old muco-pus, and in only 3 per cent. of those without mucus or pus. (*Med. Journ. of Australia*, June 4th, 1921.)

Dosage.—In mild cases, 10 c.c. of the serum should be injected subcutaneously at intervals of six to ten hours, while necessary. In severe cases doses of from 40 c.c. to 60 c.c. may be administered.

ANTISTREPTOCOCCUS SERUM.

(Polyvalent)

This serum is obtained from the blood of horses that have been immunised with increasing doses of various strains of the streptococcus, both hæmolytic and non-hæmolytic, derived from a wide variety of typical cases of acute streptococcus infection, *e.g.*, puerperal fever, erysipelas, scarlet fever, pseudo-diphtheria, endocarditis, etc., so that it is a truly representative polyvalent serum. In the treatment of septic infections it is essential to employ a serum elaborated after the injection of as many of the numerous strains of streptococci as possible.

This is an antibacterial serum with bacteriolytic and bacteriotropic properties, and it is indicated as a therapeutic agent in cases in which the streptococcus is the predominating etiological factor, such as general septicæmia, endocarditis, erysipelas, puerperal septicæmia,

streptococcus tonsillitis, scarlet fever, wound infections, and the septic complications of tuberculosis, influenza and other diseases. It is also indicated in other conditions in which the streptococcus is suspected of being the cause although its presence has not been determined, also as a prophylactic measure before and after abdominal operations of all kinds, and in cases of difficult labour where septic complications seem probable.

As the serum possesses a relatively limited quantity of antibodies it is essential to employ sufficiently large and frequent doses and the earlier treatment is commenced the better is the prognosis. Disappointing results from the use of this serum are often attributable to insufficient dosage.

Dosage.—When the toxæmia is very slight, a subcutaneous or intramuscular injection of 10 c.c. of the serum every eight to twelve hours, may suffice; but in severe cases it is necessary to give (preferably intravenously) from 20 to 40 c.c. or more, every six to eight hours, in order to obtain satisfactory results. Some authorities consider that a dose of from 50 to 100 c.c., repeated if necessary, is better than a series of smaller doses. The possibility of previous sensitisation to horse serum must be borne in mind, and if such is found to be the case, the serum (diluted with sterile saline solution, if thought advisable) must be given in small portions at brief intervals.

In order to reduce the risk of septic complications after abdominal, rectal or other operations, it has been recommended that 10 c.c. of antistreptococcus serum should be given on each of the three days previous to the day of operation.

Some physicians prefer to administer the serum mixed with twice its volume of normal saline solution as a rectal injection, the bowels being first cleansed by aperients and the rectum by enemata of warm saline solution. This method avoids the discomfort of subcutaneous injection.

One writer states that he has found that injecting the serum into the spinal theca gives the best results. By this method smaller doses may be employed, and a more prompt effect is obtained than even by intravenous injection. (*Journal of Laryngology*, April, 1919.)

Good results have been reported from the oral administration of antistreptococcus serum in acute pulmonary disease. In some cases the author used both oral and subcutaneous methods, and failed to perceive any difference in the ultimate effect (*West London Medical Journal*, January, 1923.).

In cases of acute puerperal infection, Murray advocates the intravenous injection of antistreptococcus serum in large doses—50 c.c. diluted with at least an equal volume of normal saline solution. If

no improvement results in 12 to 24 hours the injection should be repeated, using, if possible, serum from another laboratory (*Brit. Med. Journ.*, 1920, II., 270).

In the *Journal de Méd. de Bordeaux* for January 25, 1921, a report appears of two cases of erysipelas in infants which were cured by the local application of antistreptococcus serum, and of a third in which the subcutaneous injection of serum was supplemented by its topical application. Two of the cases relapsed when the local treatment was suspended, but soon recovered after its resumption. The serum was applied over the area affected three times daily, until the condition cleared up (about a week).

A writer in the *British Medical Journal* of September 8th, 1923 (p. 414), reports two cases of erythema nodosum which cleared up rapidly after the injection of 10 c.c. of polyvalent streptococcus serum on two occasions with an interval of 48 hours between. In the one case there was a history of rheumatism and slight sore throat; in the other, the erythema developed after an attack of septic tonsillitis.

Radvanyi states that better results in the treatment of acute and chronic articular rheumatism have been obtained from the use of antistreptococcus serum than from any other medicine. Chronic cases, if not cured, are materially improved, and in acute cases an endocarditis will heal more rapidly. Since the serum may render acute a chronic inflammatory process, Radvanyi says it should be used with caution in pericarditis, marked pleurisy, or advanced mitral stenosis. In acute cases, single doses of 5 c.c. should be employed; for chronic cases, several periods of treatment are necessary. (*Lancet*, June 18th, 1921, p. 1326.)

ANTIDIPHThERIA SERUM (Paton).

Paton, in his book on "Hormone Therapy by Sera, Vaccines and Drugs" (Baillière, London, 1922), points out that antidiphtheria serum contains, in addition to the specific antibody (antitoxin), a concentration of those elements of normal serum which serve for the defence, repair and maintenance of function of all the tissues.

The secretions of the endocrine glands pass into the blood stream and by their action on the nervous system control the processes necessary for the maintenance of the integrity and function of the tissues, for their defence against physiological or pathological dis-integrating forces and for their repair.

Normally, the supply of the various hormones in the blood is not great, but a serum such as antidiphtheria, which is the result of a long series of gradually increased doses of toxin, contains the quantities accumulated to meet the extraordinary demands of the tissues attacked, and is much more efficient than normal serum. The presence

of elements which produce tissue immunity is evidenced by the fact that the serum of a horse which has by graded stages been enabled eventually to withstand massive doses of diphtheria toxin is sometimes found to have a very low antitoxin content, so that the horse's immunity would appear to be due to elements other than the antitoxin, which elements will be available for therapeutic purposes.

In the treatment of diphtheria, Paton says, not only should a serum of high antitoxin potency be given intramuscularly or intravenously for its antitoxin effect, but the weaker serum should be given orally at four-hour intervals for its hormone effect. This combined treatment greatly reduces the number of antitoxin injections that will be required, as under it improvement takes place more rapidly than under injections alone.

The usual dose of Paton's serum is 1 drachm (3.5 c.c.) in water every three hours. In other conditions, such as severe traumatism with shock and collapse, or in acute inflammatory conditions, from 2 to 3 drachms (7 to 10.5 c.c.) may be given at first. In chronic cases administration may be continued for weeks with good effect.

HEMOPLASTIN.

(Hæmostatic Serum)

Hemoplastin is a sterile fluid derived chiefly from blood of horses and cattle. It is composed principally of prothrombin and thrombokinase together with a third substance known as anti-antithrombin. These constituents are in physiologically balanced solution ready for immediate use, preferably by subcutaneous injection, to increase the coagulation power of the blood, so that hæmorrhage may be avoided or arrested, according as the preparation is used prophylactically or remedially. Hemoplastin reduces the coagulation time of the blood in normal individuals as well as in hæmophilic subjects.

Physiologists explain the normal fluidity of the blood by assuming the presence of a substance, antithrombin, which prevents the formation of thrombin from prothrombin—a constant constituent of the blood. Without thrombin, fibrinogen—another constant constituent of the blood—cannot assume the insoluble sponge-like form of fibrin, the immediate antecedent of the clot.

Blood that escapes from the vascular system through injury to the vessel walls is deprived of its fresh supply of antithrombin; in other words the check upon the conversion of prothrombin is removed and, at the same time, the so-called "tissue-coagulins" or thrombokinase from the injured tissues mix with the escaping blood, hastening the formation of fibrin.

There are, however, various conditions which may to a certain extent interfere with the natural sequence of reactions, and either prevent or delay the formation of the clot. If antithrombin is in great excess, or if prothrombin is deficient, the changes are delayed, as they are also by deficiency in either thrombokinase or calcium.

Even in persons whose blood is normal in every respect it is sometimes desirable to stimulate or reinforce the processes leading to clot formation; as, for example, when an operation is impending, or if an accident has occurred of so serious a nature as to involve extensive hæmorrhage. In hæmophiliac individuals such a proceeding is of even greater importance.

For the provision of an ideally complete hæmostatic agent three substances are necessary, namely, prothrombin, thrombokinase and something that will neutralise the antithrombin that may be preventing the physiological action of the coagulating principles present in the patient's blood. It has been found possible to produce this neutralising substance, which is not a constituent of normal blood, and to it has been given the name "anti-antithrombin." These three essential factors—prothrombin, thrombokinase and anti-antithrombin—are associated in Hemoplastin in physiologically balanced proportions.

Before Hemoplastin is supplied for the use of physicians its efficiency is established by physiological test. The standard required is that it must, within the space of two hours after being injected into the vein of a dog, reduce the coagulation time of that dog's blood to one-third of what it was found to be before the injection. In this procedure it is observed that a noticeable reduction takes place in 30 minutes after the intravenous injection, while the maximum effect is attained in from 1 to 2 hours; thereafter its influence gradually diminishes.

Extensive experiments have proved that neither Hemoplastin nor anti-antithrombin alone, when administered intravenously, even in relatively large doses, will bring about *intravascular* clotting.

It must be borne in mind that the hæmostatic action of Hemoplastin is limited to its power of increasing the coagulability of the blood. It has no action upon the blood vessels, and in some cases of hæmorrhage it is the atonic condition of the blood-vessels that prevents a timely cessation of the blood flow. In such cases the use of Adrenalin or Pituitrin is indicated.

Apart from cases of hæmophiliac hæmorrhage in which it is clearly indicated, Hemoplastin is employed to advantage in pulmonary hæmorrhage, purpura hæmorrhagica, intestinal bleeding, hæmorrhage of the new-born, and hæmorrhage incidental to various surgical procedures, such as bone operations, intracranial surgery, herniotomy, tonsillectomy, hysterectomy, amputations and dentistry.

Some have reported satisfactory results from the topical application of Hemoplastin on a piece of gauze or cotton, but the more rational use is by injection.

Dosage.—The average dose for a normal individual is 2 c.c.; in hæmophilic subjects it is as well to give 5 c.c. Should bleeding persist the dose may be repeated every four to six hours until perfect control is obtained, due regard being had to the fact referred to above that the blood vessels themselves may need toning up.

As a *prophylactic* of operative hæmorrhage, 2 c.c. should be injected from 1 to 2 hours before the operation. The dose may be repeated afterward if necessary.

THYROIDECTOMISED-HORSE SERUM.

This serum is obtained from healthy horses which have been partially thyroidectomised. After the animals have been operated on, and prior to the withdrawal of blood for serum collection, they are allowed to recover their normal condition so far as the loss of thyroid gland will permit.

Thyroidectomised-Horse Serum is employed in the treatment of exophthalmic goitre (Graves' disease), in which disorder there is considered to be an excess of thyroid secretion circulating in the blood. One of the functions of the thyroid is believed to be the combustion or destruction of the products of protein metabolism that are being constantly thrown into the blood stream by the life processes. In hyperthyroidism there is more secretion than is required to neutralise the waste products in the blood, and the excess, finding no matter with which to combine, becomes a disturbing, even a toxic, element.

On the assumption that the ablation of the thyroid gland would permit excessive accumulation of waste products in the circulation, and that the blood of animals so treated, when administered to hyperthyroid patients, would furnish matter that would combine with and render harmless their excess of thyroid secretion, some years ago a preparation known as Thyroidectin, which consists of the dried blood of thyroidectomised animals, was introduced. More recently, in the belief that the neutralising substances reside in the blood serum, that portion has been separated and is available for hypodermic or oral administration.

Dosage.—The oral dose is from 1 c.c. upwards, diluted with water or wine and taken three times daily. Hypodermically, 1 to 2 c.c. may be injected two or three times a week. The proper dose must be arrived at by the observed effect of gradually increased doses, and when determined should be maintained at a point just sufficient to control the symptoms.

ERYSIPELAS AND PRODIGIOSUS TOXINS

(Coley's Mixed Toxins)

Though this preparation does not belong to the serum class, it is a bacterial product of great interest. It consists of a mixture of the toxins and derivatives of *Streptococcus erysipelatis* and *Bacillus prodigiosus*, which organisms are grown separately, the mixture being diluted to a definite strength as determined by the percentage of protein contained. Its use is recommended in cases of inoperable sarcoma, or in operable sarcoma where such operation would involve the loss of a limb, and as a prophylactic against recurrence following operation.

In the *Proceedings of the Royal Society of Medicine* for November, 1909, Coley reports the successful treatment of 52 cases of inoperable sarcoma, of which 35 had remained free from recurrence for from five to sixteen years, in addition to a large number of cases successfully treated by other surgeons (also see *Lancet*, 1909, II., 173; *Annals of Surgery*, 1914, II. 537).

The toxins are administered by hypodermic injection into the buttocks or pectoral region, though when the tumour is in an accessible position Coley considers it beneficial to give alternate injections into the tumour itself, but at first the amount so injected should only be one-quarter or one-half of that used elsewhere.

In every case of sarcoma a very small dose must be given at the outset, not more than 1/4 minim (0.015 c.c.) for an adult, and for a child proportionately less according to its body weight. To obtain these small doses a drop of the toxin mixture should be diluted with recently boiled water and a proportionate quantity of the dilution used.

The dose should be gradually increased by 1/3 to 1/2 minim (0.02 to 0.03 c.c.) if injected outside the limits of the tumour, but by less if injected into the tumour itself, until the desired reaction is obtained—a temperature of 102° to 104°F. (39° to 40°C.) with or without a chill. The more highly vascular the tumour, the more severe is the reaction likely to be, therefore the smaller should the dose be. A dose is to be given daily or on alternate days. If no improvement has occurred by the end of four weeks, it may be wise to abandon the treatment.

When the toxins are used after an operation, as a prophylactic against recurrence, small doses are the rule—only sufficient to cause a slight rise of temperature—given three or four times weekly for at least six months, with occasional intervals of a week or two.

TUBERCULIN.

The word "tuberculin" is a generic term which embraces a large variety of preparations made from the tubercle bacillus, such as T.O. (Old Tuberculin), T.B.E. (Tubercle Bacillary Emulsion), T.R., P.T.O., B.F., &c., &c. Of these various products, T.O. and preparations thereof and T.B.E. in different dilutions, are supplied by Parke, Davis & Co., London.

Essentially, tuberculin is made from a culture of *B. tuberculosis* and is used for the diagnosis of suspected cases, or for treatment of patients suffering from tuberculosis. The presence of tubercular foci in a patient so sensitizes him to the tubercle products that Old Tuberculin, applied in small amounts cutaneously or subcutaneously, elicits a distinct local or general reaction, whereas it has no effect in non-tuberculous individuals.

Diagnosis.

T.O. (Tuberculin, Old) is that form of tuberculin employed in diagnosis. It is made by Koch's original process, namely, growing tubercle bacilli in bouillon containing 5 per cent. of glycerin for several months, filtering out the bacilli, and concentrating the culture filtrate over flowing steam to one-tenth of its original volume. The finished product thus contains glycerin, and in sealed ampoules it keeps for years.

For diagnosis in human subjects, Old Tuberculin is usually applied by one of three methods: inunction with Tuberculin Ointment (the Moro method); application of tuberculin to a scarified area on the skin (the von Pirquet method); or instillation of the tuberculin on to the conjunctiva (the Calmette method).

The Moro method is the simplest, but it is not considered quite so reliable as the scarification method of von Pirquet. Tuberculin Ointment, about the size of a pea, is rubbed into the skin of the chest or abdomen in a space of about four square inches. If tuberculous, the patient will react by developing on the second day a number of small papules at the spot treated.

The von Pirquet test is usually applied to the inner aspect of the forearm. The skin is cleansed with ether, and Old Tuberculin dropped on two places about four inches apart. With a lancet a scarification is made midway between these two drops, also through the drops themselves, and the tuberculin is allowed to remain for five minutes. No dressing is applied. In about 24 hours, if the patient is tuberculous, the two spots will be more or less raised and inflamed, and the control spot should show no sign.

For the ophthalmic test, a 1 per cent. dilution of Old Tuberculin (prepared by dissolving a tuberculin disc in 5 minims [0.3 c.c.] of

distilled water) is instilled in one eye of the patient, the other eye serving as a control. In positive cases a reaction, indicated by redness, lachrymation, swelling, and the appearance of a fibrinous exudate at the caruncle of the treated eye, usually begins to appear in the course of three or four hours, reaching its height in six to twelve hours, after which it gradually disappears.

The value of the cutaneous test is somewhat vitiated by the fact that persons with healed tuberculous lesions may react, but in these cases the reaction is usually delayed beyond 36 hours. The promptness of the reaction is more significant than its extent; even though the reaction may be slight, if it comes on within 24 hours, the case is one of tuberculosis requiring treatment.

Treatment.

Tuberculin Bacillary Emulsion (T.B.E.) is extensively used in the treatment of tuberculosis. For full particulars regarding the employment of T.B.E., see section on "Vaccine Therapy," pages 57 to 59.

PHYLACOGEN THERAPY.

Phylacogens are specific bacterial derivatives antigenic in nature. They are prepared by growing the bacteria in artificial culture media, filtering out the bacteria, and combining the filtrates in definite proportions. Thus Phylacogens are culture filtrates of pathogenic bacteria. Every effort is made to ensure the use of strains of a high antigen-producing capacity, and the finished product is subjected to searching tests to determine its sterility.

As it is recognised that infectious processes are frequently the result of the invasion of the tissues by several types of organisms, each Phylacogen is prepared from two, or more, species of bacteria—the species commonly represented in the pathological condition for the treatment of which that particular Phylacogen is recommended. The bacterial derivatives from these cultures are combined in proportions corresponding as nearly as possible to the relationship which the organisms bear to each other in the pathological condition to be treated.

There are six varieties of Phylacogen, and each of them is administered by subcutaneous or intravenous injection. Intramuscular injections are not recommended. The following scheme of dosage applies to all the varieties unless otherwise specified.

The first injection should invariably be given subcutaneously in order to establish the tolerance of the patient, and should be made as slowly as possible. Temperature and pulse rate should be noted before treatment is commenced.

Subcutaneous Doses.

It is important that the dose should be adapted to the individual requirements and conditions. For feeble or aged patients, also for infants, the initial dose should be one-fourth to one-half the adult dose. Too large an initial dose should be avoided ; in the case of the average adult the initial dose for subcutaneous injection should be 0.5 to 1 c.c., and in subsequent doses, given every two or three days, the amount should be increased by 0.5 to 1 c.c. according to the condition of the patient, the character and extent of the disease, and the promptness with which the patient responds to the treatment. In the event of an excessive reaction, it may be well to delay the next dose for a longer period and then to give only the amount which produced the reaction until it is found that an increased dose can be tolerated. It is not usually necessary to give more than 5 c.c. for a single subcutaneous dose.

Intravenous Doses.

The initial intravenous dose should not exceed 0.125 to 0.25 c.c. (say 2 to 4 minims), and this should always be preceded by one or more doses subcutaneously. Subsequent doses may be increased by 0.125 to 0.25 c.c. until an amount of 1 c.c. is reached, after which the dose may be increased by 1 c.c., paying due regard to the general indications of the patient and endeavouring to avoid the production of a marked constitutional reaction.

For the administration of small doses intravenously it may be desirable to dilute the Phylacogen with warm physiological salt solution.

Interval Between Doses.

The usual interval between doses when no marked systemic reaction occurs, is from two to three days. In pneumonia, also in typhoid fever and surgical infections, it is occasionally advisable to repeat the dose more frequently. No hesitation need be felt in reinjecting when the pulse has resumed the rate observed before the previous injection.

To obtain the best results with Phylacogen in acute infections it is urged that the appropriate Phylacogen be used as early in the course of the disease as possible.

The Phylacogens are supplied in 10 c.c. vials with rubber diaphragm caps, and in most cases in sealed ampoules containing 1 c.c. To withdraw Phylacogen from the diaphragm vial apply a suitable disinfectant to the cap, plunge the syringe needle through the rubber, invert the bottle, and draw off the required quantity of liquid into the syringe.

Contra-Indications.

Intravenous injections of Phylacogen should never be given to terminal cases (those of patients already dying); hopeless cases; cases with severe dangerous cardiac involvement; nor to cases with pronounced arterio-sclerosis, high blood-pressure or nephritis.

To the *subcutaneous* administration of Phylacogen there is no contra-indication, unless it be nephritis. In the presence of grave heart lesions of long standing, care should be exercised in the gradual augmentation of the dose.

RHEUMATISM; PHYLACOGEN.

Rheumatism Phylacogen contains derivatives from cultures of *Streptococcus* with a proportion of those from *Staphylococcus* (*albus* and *aureus*). Its administration is calculated to stimulate resistance to infection due to the less virulent forms of streptococci, notably the *Streptococcus salivarius* and *Streptococcus faecalis*. Thus it is indicated for the relief of such conditions as are variously called "acute rheumatic fever," "acute articular rheumatism," "acute inflammatory rheumatism," "chronic rheumatism," "rheumatic arthritis," "rheumatic myalgia," "rheumatic neuralgia," "rheumatic iritis," "myositis," "fibrositis," "lumbago," "sciatica," etc.—most of which may be regarded as clinical manifestations of toxic infection by certain types of this micro-organism.

Experience has shown that the administration of Rheumatism Phylacogen is, in many cases, followed by relief from pain, by disappearance of swelling and redness, and by ability to move the affected joints freely in cases of acute arthritis, and in chronic cases equally good results have been obtained. In those cases where some improvement is apparent, it should always be the rule to continue treatment until the disability entirely disappears.

MIXED INFECTION PHYLACOGEN.

Mixed Infection Phylacogen is a sterile aqueous solution of bacterial derivatives from cultures of *Streptococcus* (hæmolytic and non-hæmolytic), *Staphylococcus* (*aureus* and *albus*), *B. coli communis*, and *Pneumococcus* (four types). The administration of this preparation is indicated in the treatment of a great number of cases of complex infection, such as infected wounds, puerperal sepsis, infections following surgical operations, fistulæ and septicæmias generally.

In treating surgical infections of any kind it should be understood that Phylacogen does not cause the absorption of pus or the disappearance of pockets or collections of pus. These should be sought for, treated surgically, and the pus evacuated. A temporary increase of pus discharge from open wounds which are infected seems to be a

frequent result of the injection of Mixed Infection Phylacogen. In cases of infected wounds or peripheral phlegmons, physicians should note that regardless of whether or not the temperature drops to normal after the first few injections, the treatment must be continued until the entire infected area shows healthy granulations. This is particularly important in deep-seated infections of the arm or leg if relapses are to be avoided.

The duration of treatment necessarily depends largely upon the character of the disease, the extent of involvement, and the promptness with which the patient responds to treatment.

PNEUMONIA PHYLACOGEN.

Pneumonia Phylacogen contains derivatives from cultures of *Pneumococcus* (four types) and *Streptococcus* (hæmolytic and non-hæmolytic).

In the treatment of acute inflammatory conditions of the lung with Pneumonia Phylacogen it can only be expected that the pneumonia, as such, will be relieved; sequelæ, such as pleurisy with effusion, empyema and pulmonary abscess, will require the usual surgical intervention and drainage.

The initial dose should be 1 c.c. injected subcutaneously; for debilitated patients 0.5 c.c., and for infants or the aged 0.25 to 0.5 c.c., is sufficient. Subsequent doses, given daily, may be increased by 0.5 to 1 c.c. according to the effect produced on temperature and pulse-rate by the previous dose. In some cases of pneumonia little effect will follow even large doses of Pneumonia Phylacogen given subcutaneously. Clinical experience in such cases has been that 1 c.c. given intravenously will often lower the temperature to normal. Subsequent doses should be given subcutaneously, in the amounts suggested previously.

The evidence of a large number of clinical reports is to the effect that where Pneumonia Phylacogen is administered early, the results have on the whole been good.

In more advanced cases, Phylacogen treatment may be useful but is less hopeful.

GONORRHOEA PHYLACOGEN.

Gonorrhœa Phylacogen contains derivatives from cultures of *Gonococcus*, *Staphylococcus* (*aureus* and *albus*) and *Streptococcus* (hæmolytic and non-hæmolytic). Its use is indicated in the treatment of the various forms of chronic gonorrhœal infection. Clinical experience warrants the conclusion that this Phylacogen will relieve many cases of true gonorrhœal arthritis, and that other sequelæ of gonor-

rhoeal infection such as epididymitis, vesiculitis, cystitis, vaginitis, cervicitis, endometritis, salpingitis, gonococcal ophthalmia and iritis, etc., will often yield to this form of treatment.

The effect of Phylacogen treatment of gonorrhoeal urethritis, either acute or chronic, is doubtful.

ERYSIPELAS PHYLACOGEN.

Erysipelas Phylacogen contains derivatives from cultures of *Streptococcus* derived from cases of erysipelas, also a proportion of those from cultures of *Staphylococcus (albus and aureus)*. It has been successfully used for the treatment of a large number of cases.

In the administration of Erysipelas Phylacogen the principles indicated in the paragraph dealing with dosage should be followed. If the patient is in a grave condition and the reaction following the first subcutaneous dose is not excessive, three subsequent doses of the same amount as the first may, in the absence of contra-indications, be given at intervals of twelve hours. If a case of erysipelas does not show marked improvement after three or four subcutaneous injections of Erysipelas Phylacogen, it is suggested that intravenous medication should be resorted to.

TYPHOID PHYLACOGEN.

Typhoid Phylacogen contains derivatives from cultures of *B. typhosus* and, in less proportion, *B. paratyphosus (A and B)*.

In a disease running so acute a course as that of typhoid, the action of a bacterial vaccine is too slow to bring about striking results. Somewhat better effects have been produced by the administration of Typhoid Phylacogen which, while acting in a manner similar to that of a vaccine, presents the antigens in a condition to act immediately upon the defensive powers of the system. It is highly desirable that the Phylacogen should be administered as early as possible, before the capacity of the body cells to respond to the stimulus become seriously impaired.

The dosage for the administration of Typhoid Phylacogen should be as indicated above except when the patient is in a grave condition. As a routine procedure the interval between doses should not be more than three days. In the case of patients who are very much exhausted, and in desperate cases, the initial dose should be very small and increased as tolerance is established. The dose for a child from one to ten years of age should be 0.5 c.c. to 3 c.c. subcutaneously, increased by 0.5 to 1 c.c. at each injection. An infant may safely be given 0.5 c.c. of the Phylacogen subcutaneously. If the intravenous route is chosen in a case of typhoid fever the initial dose should not be more than 0.125 c.c. (2 minims), and the dose should be doubled every twenty-four hours until the toxæmia is controlled.

GLAND THERAPY.

GENERAL SURVEY.

The use of animal extracts in medicine is as old as medicine itself. As early as 600 B.C. an orchitic extract is reported to have been administered in the treatment of obesity. The ancient Egyptians certainly made use of such products. The practice flourished in the time of Hippocrates, and both Galen and Celsus testify to the antiquity of organo-therapy. The ancients appear to have used these agents, calculating that their vile taste and nasty odour would drive away the offending disease. That superstition must have played a large part is well demonstrated when we read that Pliny advocated the use of some fifty preparations from the hyæna in the treatment of as many diseases in man. In spite of the fact that the first Pharmacopœia, published by the College of Physicians in 1618, contains several preparations of animal extracts, it is only within the last thirty years that this class of remedies has been carefully studied and scientifically applied. During this comparatively short time a vast amount of work has been done. Many previously perplexing diseases have thereby been explained, and some remarkable results have been accomplished in the therapeutic application of the glandular preparations.

One of the most interesting phases of animal physiology is the control exerted by the ductless glands over the various body functions. As far back as 1776, Holler, in discussing the anatomy of the thyroid, classed together the thyroid, thymus, and spleen as "glands without ducts which manufacture a special fluid which is received into the veins, and so restored to the general circulation." The term "ductless" is applied to those glands—namely, the suprarenal glands, the pituitary body, the thyroid and parathyroid glands, the thymus gland, the pineal body, the spleen, and some smaller glands such as the carotid body—which, while they elaborate substances that find their way into the circulation, have no special duct for conveying the secretion, such as have the liver and the glands of the skin and digestive tract. The products of the activity of these ductless glands pass into the blood-stream, either directly or by way of the lymphatic system, and are therefore described as internal secretions.

In its deepest significance, it is probable that every cell in the body is a potential ductless gland, and has some slight influence on the life and function of its fellow cells. The terms "ductless gland," "gland of internal secretion," and "endocrinous gland," are, however, restricted to those organs which consist of what is called "glandular tissue," yet have no ducts for discharging the substances which they secrete.

The term "internal secretion" was first used by Claude Bernard in reference to the glycogenic function of the liver. We must, however, regard the term as a misnomer in this instance, as the liver, so far as glycogen is concerned, is really only a storage mechanism.

It is to the work of Brown-Séquard on testicular extract, Ord and others on the thyroid gland, and the more definite results of Bayliss and Starling in their investigations, that we owe the foundation of our knowledge of the real nature of the internal secretions, the modern conception of the term implying "secretions produced by the cells of certain organs or glands not passed on to any free surface, or by any duct, but carried away by the blood or lymph stream to act specifically elsewhere in the body."

The internal secretions of the ductless glands, with the exception of the spleen, belong to the class of bodies known as "hormones," a term devised by Starling to designate the active principles of the internal secretions, and this word, which, literally, means "stimulator," has passed into general use, and is likely to remain as the most popular description of these principles.

Among the important functions depending upon the glands of internal secretion are sexual development, ovulation, fat distribution, skeletal growth, and other body functions. Although the several glands are situated widely apart in the body, and have no visible connexions, they constitute a unified system, each member of which has its special function or functions and contributes to the maintenance of a complex interrelation.

It is now established that there exists not only an organic and functional harmony between the glands, but a compensatory interaction also. If organic disease or abnormality interferes with the function of a gland, the deficiency appears in some instances to be made up by the action of one of the other glands, but in other instances the imperfect action of one gland may disorganise the metabolism of the entire system. The establishment, therefore, of what has been described as the "hormone balance" is of the utmost consequence to the individual, and constitutes a most important phase of hormone therapy. For it must be remembered that when a certain secretion is deficient it is necessary to deal not only with the deficiency but also the baneful effects of an uncontrolled antagonistic secretion.

Much of our knowledge of the functions of the ductless glands has been derived from the study of the symptoms observed in human beings in whom one or other of the glands is diseased. These functions must necessarily be studied under the following headings:—

- (1) The effects of disease in these glands in man, noting, on the one hand, the conditions associated with hypertrophy and, presumably, increased secretion (though hypertrophy does not

always signify increased secretion), and, on the other, conditions associated with atrophy, when the secretion is diminished or absent ;

- (2) The effect of their extirpation in animals, and
- (3) The effects of extracts of the glands, either upon normal animals or as therapeutic agents in man.

It is a matter of considerable anatomical interest that the ductless glands, for the most part, are extremely well protected from injury. The pituitary gland, for example, rests at the centre of the skull, the pineal gland is situated near the centre of the brain, the parathyroids are embedded in and behind the thyroid glands deep in the neck ; while the suprarenals are padded in fat above the kidneys.

While some of the glands appear not to be essential to life, *e.g.*, the testes and ovaries may be removed without fatal consequences, the removal of others experimentally, by accident, or through necessary operative procedures, results in distressing, and in some cases fatal, consequences. For example, the removal of the suprarenal glands rapidly leads to the death of the animal or patient. The removal of the parathyroids causes an accumulation in the blood of toxic substances which, presumably, are, in the ordinary course, neutralised by the action of the glands. Similarly, the removal of the pancreas leads to diabetes, and later to death.

Many of these glands are subject to disease, notably tuberculosis and cancer, and, although the whole gland is not necessarily destroyed, the secretion is altered, and there follows a disturbance in the equilibrium of the body, which may manifest itself as an increased or decreased function. For example : increased function of the anterior lobe of the pituitary gland is accompanied by overgrowth of the body, especially of the skeletal parts ; decreased function is associated with retrogressive changes in the reproductive organs ; adiposity is also a feature of hypopituitarism. Abnormal activity on the part of the thyroid is responsible for that type of goitre known as Graves' disease, while decreased function results in the well-known condition of myxœdema in adults and cretinism in children.

It is obvious, therefore, that the failure of these glands to perform their proper functions may produce pronounced pathological states of the body, and we are led to a consideration of hormones in the treatment of such conditions.

Preparations of the ductless glands derived from cattle, sheep, or other animals, are employed in the treatment of diseases due to destructive changes in the glands themselves, a form of treatment which is known as "substitution therapy," the object being to replace the absent or deficient secretion of the gland involved. The

administration of carefully selected and prepared glandular products is also likely to prove beneficial where there is relative insufficiency owing to overaction of some antagonistic gland.

It sometimes happens that the system requires a greater amount of glandular secretion than the gland is capable of supplying, as, for example, in simple goitre of the parenchymatous type.

Occasionally, a gland may be developing an amount of secretion in excess of the system's requirements, in which case its activity may be controlled by the administration of another glandular preparation. A good example is the indication for Mammary Substance in cases of ovarian irritability or hyperactivity. There are also cases where the well-known physiological action of the various glands may be useful, quite apart from any defect in the patient's own glands. Lastly, a large number of conditions exist in which glandular products have been found beneficial, notwithstanding that no connexion has been established between the disease and the gland function. Such medication may be classed as "empirical treatment."

It is an important point in estimating the possibility of the successful application of hormone therapy to know how urgent the body's need for the secretion is, and the length of time the latter remains in the body. Light on these questions has been obtained by determining how soon symptoms appear after the removal of the glands. For example, after removal of the thyroid it has been found that symptoms may not appear for weeks, whereas they appear within two or three hours after the removal of the pancreas. It is evident that the chances for successful treatment are much more favourable in the former case. Furthermore, the thyroid, according to Dale, is the one ductless gland which fulfils all the criteria necessary for successful substitution therapy, namely, that the gland from which the extract is prepared must contain the hormone in an amount much in excess of the body's immediate needs, while the hormone must be fairly stable so as to resist chemical changes during extraction, and be capable of absorption from the alimentary canal. At the same time, it must be possible for intermittent doses to replace satisfactorily the constant slow secretion which normally occurs.

It follows, therefore, that there are marked differences in the character of the internal secretions themselves. Fortunately, hormones are not necessarily destroyed by boiling, so that sterile solutions can be prepared for hypodermic administration. While a chemically pure active secretion of a gland is very desirable, it is not essential. In only a few instances has it been possible to isolate the active principle, and in most cases the glands themselves, or extracts of them, are employed.

From this brief survey of the rationale of hormone therapy it will be obvious that its uses are many, and its application logical.

Increased knowledge of the functions of the ductless glands, and their relations to each other, must, of necessity, open up fresh fields of scientific prescribing, to the advantage, no doubt, of the reputation of medicine as an exact science.

In the following pages some particulars are given of the various preparations of internal secretion which are offered by Parke, Davis & Co. with full assurance of their identity and quality, also references to their therapeutic applications, which amply demonstrate the great importance of ductless gland therapy in the treatment of functional disorders.

THE THYROID.

Notwithstanding the popularity of some of the more recently introduced glandular preparations, thyroid medication may still be said to occupy the foremost place in organotherapy, from the fact that the indications for thyroid treatment are so much more numerous than those for other glands, however important these may be. This is due to the fact that the functions of the thyroid probably have more ramifications than those of any other endocrine gland. The thyroid has an important bearing on the whiteness of the teeth, the distribution of the hair, the moisture of the skin, the distribution of fat, the development of the genital function, the stability of the mind, the speed and efficiency of proteid metabolism, and the ridding of the body of protein poisons, especially bacterial.

The relationship of the thyroid to the sex glands, particularly to the ovaries, appears to be especially intimate, so much so that normal ovarian development and normal ovarian function are scarcely possible if thyroid secretion is not normal.

Many cases of sexual infantilism, with its amenorrhœa, dysmenorrhœa and delayed somatic and psychic development, may be attributed to varying degrees of subthyroidism.

If the thyroid gland fails to discharge its functions in the normal way, a very varied symptom complex may arise, but specific measures have been developed for the treatment of disordered conditions associated both with deficient function (hyposecretion) and with excessive secretion (hypersecretion).

HYPOSECRETION.

The three classical types of disease due to decreased thyroid secretion are **infantile cretinism**, **cachexia strumipriva**, and **myxœdema**.

Those disorders are characterised chiefly by physical and mental inertia; decreased metabolism; abnormal sensations of taste, smell, and hearing; subnormal temperature; slow, weak pulse; changes in the skin (dryness, abnormal pigmentation); falling and blanching

of the hair; and tendency to obesity. In the infantile type, physical and mental development are greatly retarded, and unless the thyroid deficiency is supplied children suffering therefrom become dwarfed and idiotic. The changes in the skeleton are particularly marked. There is an inhibition of the normal ossification of the cartilages. The epiphyseal ends of the long bones grow slowly while the periosteal ossification may be normal or even in excess. The extremities are relatively short and thick, and the pelvis is small. The metabolism is decreased more in thyroid disease than in any other known condition.

In addition to the above clear-cut effects of diminished secretion of the thyroid, there are a number of phases of hypothyroidism of less severe manifestation. Certain cases of **anæmia, chlorosis, hæmophilia, mental disturbances, migraine, fatigue from slight exertion, arthritis and other rheumatoid conditions, delayed union of fractures**—all these have been correlated by various investigators with deficient secretion of the thyroid.

In the treatment of the three typical forms of thyroid insufficiency, the use of thyroid preparations has been attended with strikingly good results. The early administration of a thyroid product in cretinism enables the children to develop normally, both physically and mentally. The gland substance must, however, be administered over a period of many years, often during the entire lifetime of the patient.

With the other conditions which have been more or less loosely associated with thyroid hyposecretion (thyroid insufficiency) the results, as might be expected, have been more or less irregular. Thyroid therapy is not to be regarded as a panacea for all of the ills which have been described in connexion with thyroid disturbances, but its intelligent application will often prove of great benefit in some of the more or less obscure types of thyroid insufficiency.

Obesity is frequently, but not necessarily, associated with decreased thyroid activity; the carefully controlled administration of a reliable thyroid preparation will quickly produce satisfactory results in cases of true subthyroid obesity. The obesity of mild and moderate degrees of hypothyroidism, however, should not be confused with myxœdema, the hard puffy swelling, usually of the face and hands, which is characteristic of extreme hypothyroidism. The thyroid hormone is not only the great detoxicator of the products of proteid metabolism, but the great stimulant of metabolism in general. Deficiency in thyroid hormone causes a slowing down of the katabolic process, one of the results of which is the retention, and deposition in the form of fat, of large quantities of material which in the normal individual are completely oxidised and eliminated.

The basal metabolism test makes diagnosis of moderate and severe degrees of hypothyroidism comparatively easy. Some of the obvious

symptoms of thyroid deficiency are invariably present, however, especially somnolence, slowness of thought and action, dry scaly skin due to inactivity of the sweat glands, brittle nails, alopecia, constipation, subnormal temperature, and cold hands and feet.

Of the specific indications for thyroid treatment the following may be mentioned. Definite benefit from the persevering administration of full doses of thyroid is reported (*Lancet*, 1914, ii., 1295) in cases of **acute dementia** and **confusional states**, and in the later stages of recent **melancholia** when the patient has improved to a certain period and there remained. In cases of **epileptic insanity** 5 grain doses of thyroid daily for a long period brought about a substantial reduction in the number of fits.

In cases of **enlarged prostate** 5 grains of thyroid daily and decalcifying agents such as phosphoric acid are fairly effective (*B.M.J.*, 1914, ii. 864).

In the treatment of simple parenchymatous goitre of puberty and adolescence a dose of from 2 to 5 grains of dried thyroid each night at bedtime is often followed by a gradual diminution in the size of the gland (*Practitioner*, Feb. 1915, p. 266). This is probably due to the natural call for increased internal secretion at this time of life being met by a supply from an external source.

In **nocturnal enuresis** thyroid gland administration has in many cases proved of great value, the reason being that thyroid deficiency means poor nutrition of the walls of the bladder, which become unduly sensitive to stimuli, and such deficiency can be compensated for by regular thyroid treatment (*Medical Press*, Nov. 29, 1916). The same article points out that where thyroid secretion is deficient, induration takes place in the subcutaneous tissues and the growth of adenoids may be assumed to be due to this cause, and the enlargement of the tonsils to fibrous hyperplasia. A sluggish mentality and the typical conformation of the countenance will characterise cases in which the administration of small doses of thyroid may be expected to prove beneficial. The initial dose should not exceed one-sixth grain, to be cautiously increased if indicated.

In **psoriasis**, thyroid treatment, one grain or less twice daily, often proves remarkably effective (*American Medicine*, October, 1915).

Reporting a meeting of the Dermatological Society, the *Medical Press* (May 1, 1918, p. 341) refers to the case of two boys, who from birth had been affected with **fibroma molluscum**, their father having been subject to the same ever since he was eight years of age. Two other children in the family showed no signs of the disorder. In each boy the tumours disappeared under the administration of $\frac{1}{2}$ grain

of thyroid daily. At the same meeting the case was reported of a woman of 28 who for many years had been subject to extensive **xeroderma** which four years previously broke out into a dry papular pruriginous eczema. Under 1 grain doses of thyroid, concurrently with phosphate of iron and the local application of boric ointment, the condition cleared up.

Writing of **amenorrhœa** in *The British Medical Journal* (December 28, 1918, p. 705) one authority states that the obese female with scanty irregular menstruation accompanied by headaches, depression and pelvic pain may be successfully treated with desiccated thyroid in doses of from $\frac{1}{4}$ to 1 grain at bedtime for a lengthened period unless there is evidence of intolerance, in which event the dose should be reduced to one-tenth grain or the treatment may be intermitted for two or three weeks. It is sometimes beneficial to give concurrently 5 grains of ovarian substance thrice daily.

In all disorders arising from thyroid insufficiency the administration of thyroid gland substance is specific so far as amelioration or even disappearance of the symptoms is concerned; but as soon as treatment is stopped the symptoms will recur if the gland has retrogressed to such a degree that it does not respond to the stimulus of the treatment sufficiently to resume normal function. In such cases it is necessary to administer continuously a pharmaceutical preparation of the gland as a substitute for the secretion which the patient's thyroid should supply normally.

For the treatment of such cases use is made of thyroid glands obtained from healthy animals; these glands are desiccated and powdered. The therapeutic effects of the gland are generally attributed to the iodo-albuminous matter which it contains, and the amount of this differs considerably according to the age and condition of the animal from which the gland was obtained. In order to secure uniformity in therapeutic power, Parke, Davis & Co. adjust their desiccated thyroid gland to a standard of not less than 0.3% of organic iodine. Tablets prepared from this powder are supplied in a series of doses. An improved means of administering thyroid is provided in Thyroprotein (*see* p. 126), which consists of the pure proteid extracted from the gland without extraneous matter and standardised to contain 0.33% of iodine in organic combination. This product is provided in tablet form for oral administration and in solution for hypodermic use.

The administration of thyroid gland in conjunction with suprarenal gland and pituitary substance (either with or without parathyroid gland) possesses advantages in conditions where there is insufficient function of the several glands, and Suprarenal Compound Tablets or Tetraglandular Tablets may prove beneficial in such cases.

THYROID GLAND POSOLOGY.*

The dose of thyroid gland to be given in cases of thyroid insufficiency depends upon the tolerance of the patient, and varies from $\frac{1}{4}$ grain to 10 grains (16 mgm. to 0.65 gm.) of the fresh gland, or 1/20 grain to 2 grains (3 mgm. to 0.13 gm.) of the desiccated gland. In **cretinism** a good dose to begin with is 5 grains (0.325 gm.) of the fresh gland—or 1 grain (0.065 gm.) of desiccated—three times a day. The dose may be gradually increased until signs of thyroid excess appear. The most important of these signs is tachycardia; when this occurs it is a signal that the point of tolerance has been exceeded, and the dose must be reduced to the maximum quantity that will not produce this symptom.

In **myxœdema** the same procedure is followed, with the exception that much larger doses will be required. It is usually perfectly safe to begin with 10 or 12 grains (0.65 or 0.775 gm.) of fresh gland three times daily, with careful oversight, as in the case of cretinism, to determine the quantity the patient can take comfortably, and that will keep him in a fairly normal condition. The clinical improvement is always a little more prompt and pronounced if, besides the thyroid preparation, a small quantity of iodide be given, such as potassium or sodium iodide or, for patients who do not tolerate the ordinary iodides, iodalbin. To a myxœdematous patient who is getting 40 grains (2.5 gm.) of fresh thyroid gland *per diem*, it is advantageous to add 3 grains (0.2 gm.) of sodium iodide or 5 grains (0.325 gm.) of iodalbin to the daily dose.

In most of the lesser degrees of hypothyroidism, thyroid therapy frequently results in the restoration of the thyroid gland of the patient to its former normal physiological activity, this being the consequence either of direct stimulation or of recuperation resulting from the rest afforded to the exhausted gland by substitution therapy.

The dry forms of **eczema**, and indeed almost all skin diseases characterised by dryness or scalliness, are benefited by thyroid treatment. In **mentally defective children** small doses of thyroid are often useful, especially in conjunction with desiccated thymus and pituitary glands.

The dose of thyroid gland in all subthyroid conditions except cretinism and myxœdema should be very small to begin with. Thus,

* The dosage here recommended follows the custom that has been in use in this country since thyroid was introduced. By common consent, the minimum dose ($\frac{1}{4}$ grain) of desiccated thyroid in the British Pharmacopœia is much too high, and it is considered safer to adhere to the established method of giving prominence to the amount of fresh gland represented in the tablets rather than risk overdosage by basing the titles on the amount of desiccated gland. Prescribers are respectfully requested to specify "desiccated" when such is required, in order to avoid disappointment.

in the case of a mentally defective child who seems to show evidence of a need of thymus and pituitary stimulation as well as of thyroid, it is often beneficial to administer $\frac{1}{2}$ grain (0.03 gm.) of fresh thyroid gland two or three times daily, and to give at the same time 1 grain (0.065 gm.) of desiccated thymus gland and 1 grain (0.065 gm.) of pituitary whole gland.

In conditions resulting from under-nourishment in children, in cases characterised by headache, poor appetite, poor circulation resulting in cold hands and feet, rapid improvement often follows the administration of $2\frac{1}{2}$ grains (0.16 gm.) of fresh thyroid gland simultaneously with $\frac{1}{2}$ grain (0.03 gm.) of sodium iodide, or 1 grain (0.065 gm.) of iodalbin, once a day.

In cases of nocturnal enuresis, decided benefit is often conferred by the combined administration of the thyroid and pituitary glands, in the proportion of 1 grain (0.065 gm.) of fresh thyroid gland and $\frac{1}{2}$ grain (0.03 gm.) of pituitary whole gland, three times a day.

In **anæmia** and **chlorosis** the effect of iron is occasionally enhanced by the addition of small doses of thyroid. Especially in chlorosis the combination of 1 grain (0.065 gm.) of reduced iron and 1 grain (0.065 gm.) of fresh thyroid, given three times a day, will be found effective. A compound thyroid tablet, Thyrafer, consisting of desiccated thyroid, $\frac{1}{2}$ grain, desiccated suprarenal, 2 grains, and Bland pill, 1 grain, has been found to give good results in many of these cases.

Delayed puberty and **amenorrhœa** may be due, as is generally known, to defective thyroid secretion; and in these cases, too, the judicious combination of thyroid with other gland preparations to meet special indications is advantageous. For instance, in cases of delayed puberty, $2\frac{1}{2}$ grains (0.16 gm.) of fresh thyroid gland, combined with 3 or 4 grains (0.2 or 0.26 gm.) of ovarian substance, are frequently more effective than thyroid alone.

In cases of **obesity** in which hypothyroidism is concerned, the quantity of thyroid gland to be administered depends upon the tolerance of the patient and, within certain limits, should vary in direct ratio with the degree of thyroid deficiency. The best way to determine the dose is by actual trial, starting with 1 grain (0.065 gm.) of fresh gland three times a day, and giving gradually ascending doses until the point is reached at which the patient begins to show signs of thyroidism: headaches, tremors, restlessness, etc. The dose should then be reduced to an amount slightly smaller than that which produced the symptoms of thyroidism. One case may be found to need three or four times as much as another.

Dosage of Thyroprotein.—When administering this concentrated extract of the thyroid gland, only very small doses are required, namely 1/50 to 1/10 grain (1.3 mgm. to 6.5 mgm.), orally, thrice daily, or 1/50 to 1/25 grain (1.3 mgm. to 2.6 mgm.), hypodermically, governed by the reaction. In conditions depending upon a comparatively slight degree of thyroid insufficiency, doses of 1/50 grain (1.3 mgm.) are usually ample, but in cases exhibiting marked hypothyroidism the dose may quickly be increased up to 1/10 grain (6.5 mgm.), beyond which it will rarely be necessary to go.

Contra-indications.—The administration of thyroid preparations requires extreme caution in the presence of grave heart disease, and should be relinquished upon the first suggestion of tachycardia. As the drug appears sometimes to aggravate a tuberculous process, it is probably better not to employ it in the presence of tuberculosis.

HYPERSECRETION.

In all degrees of hyperthyroidism the outstanding phenomenon is an increased rate of metabolism. Most of the symptoms displayed are precisely the opposite of those which arise from hypothyroidism. The patient is keenly alert, even abnormally so, the skin is moist, and there is no obesity or puffiness.

The thyroid gland increases its secretion normally during pregnancy. This is necessary because of the increased metabolism and the increased nutrition that are called for. If the thyroid gland, for any reason, fails to heed the call of pregnancy, the woman develops signs of toxæmia, the teeth decay, the hair begins to fall out, and the nails become brittle.

The four cardinal symptoms of "hyper," or too copious, secretion are: **enlargement of the thyroid, tachycardia, tremor, and exophthalmos.** These, with other secondary symptoms, varying in character, constitute the symptom-complex of **Graves' disease (exophthalmic goitre).** The thyroid enlargement, while one of the constant symptoms, may not be very marked. The cardiac and nervous symptoms, as well as the exophthalmos, vary with the degree of hypersecretion. In advanced cases of exophthalmic goitre with marked toxæmia the nervous and cardiac disturbances are often extremely severe.

In cases of suspected hyperthyroidism which do not present clearly defined symptoms, the application of the Adrenalin test suggested by Prof. Goetsch is a useful diagnostic aid.

The serum, and also the dried blood, of animals from which the thyroid glands have been removed, have been used with some success in the treatment of Graves' disease. The removal of the thyroid gland permits those substances which have a specific power of neutralising thyroid secretion to accumulate in the blood or other body fluids;

hence the systematic administration, either orally or hypodermically, of the blood or serum of animals treated in this way frequently yields satisfactory results in controlling the thyroid toxæmia.

For the treatment of hypersecretion, Thyroidectin (prepared from the blood of thyroidectomised animals) may be administered orally. It is indicated in the symptomatic treatment of exophthalmic goitre, the object being to neutralise thyroid intoxication. The dose is 5 or 10 grains (0.325 or 0.65 gm.), according to the severity of the symptoms, to be taken thrice daily. Thyroidectomised-Horse Serum can also be used in doses of 1 to 2 c.c. orally or hypodermically.

Recent work by Professor Fraser (*British Medical Journal*, January 3rd, 1925) and others, leads to the conclusion that many cases of exophthalmic goitre are considerably improved by the administration of some form of iodine. Jackson (*Lancet*, April 11th, 1925) records the observation that the administration of iodine prior to thyroidectomy considerably facilitates operative procedures, and also that post-operative iodine treatment lessens subsequent hyperthyroidism and reduces mortality.

The use of these preparations, however, is not expected to supplant surgical or X-ray treatment, but is to be regarded as a useful adjunct to operative measures, and an aid in dealing with cases of hyperthyroidism in which, for any reason, surgical intervention is deemed inadvisable. Furthermore, in the operative treatment of exophthalmic goitre, immediately subsequent to the operation there is usually a temporary increase of the thyroid toxæmia owing to mechanical irritation. It is this temporary increase in secretion which in extreme cases renders the operative procedure more or less hazardous.

THE PARATHYROIDS.

The parathyroid bodies—usually four in number, two on each side of the median line of the body—are at the upper and lower ends of the hilus in each thyroid lobe. Generally they are to be found in close association with the superior and inferior thyroid arteries. In the human subject they are very minute, and in the cadaver appear as pigmented bodies often indistinguishable from the pigmented fat in which they are to be found. This fatty substance constitutes a large percentage of the weight of the gland and apparently possesses no therapeutic value. The parathyroids appear to be distinct bodies differing from the thyroid in origin, structure, and action. According to Scott-Williamson (*Lancet*, 1923, II., 1337), changes in the parathyroid bodies are definitely related to the nature and quantity of the secretory phase in the thyroid gland, and it is suggested that the parathyroid may act as a sort of sentinel of neuro-lymphatic nature, probably engaged in measuring the efficiency of that gland.

It is well recognised that the parathyroid receives a not inconsiderable branch from the sympathetic. According to Vines (*The Parathy-*

roid Glands in Relation to Disease, 1924), the parathyroid belongs to that group of glands which act in conjunction with the parasympathetic, and is, therefore, opposed to the sympathetic system. The thyroid, pituitary and suprarenal glands on the other hand, form the group of endocrine organs which are classed as sympathicotropic, and there is a general indication that their actions are in opposition to the parathyroid.

The distribution of the parathyroid bodies does not appear to be absolutely constant, also, as is often the case with thyroid, the glands vary in size with similar variations in the size of their associated superior and inferior arteries.

In spite of the facts that the parathyroid glands are so insignificant in size and that their individual character was not recognised until recent years, these glands form one of the most interesting and not the least important links in the endocrine chain. In addition to the possible effect which they may have on the thyroid, at least three theories have been put forward to explain their physiological action :— (1) that the parathyroid destroys guanidine, a poisonous purin body which otherwise accumulates in the muscles as the result of imperfect metabolism of proteids, in other words, it acts as a detoxicating agent ; (2) that it controls the calcium content of the blood and thereby indirectly acts as a sedative and regulator of nerve impulses ; (3) that it regulates the acid-base equilibrium of the blood, thus being a potent factor in the prevention of acidosis and alkalosis.

Physiologists would appear to lean to the first-named theory, namely, that the parathyroid destroys guanidine which, if allowed to accumulate, would produce such conditions as tetany, convulsions, epilepsy, fatigue, exhaustion, loss of weight, and lowered body resistance to irritations and infections of all kinds.

Noël Paton (*Edinburgh Medical Journal*, October, 1924) has accumulated evidence which shows that idiopathic tetany is in the nature of a toxæmia due to methyl guanidine in the blood, and concludes that the increased muscular tone which generally follows removal of the parathyroids indicates that these structures exercise an influence upon the tonus of skeletal muscles. Clinicians, on the other hand, rather favour the view of Vines and Grove (*British Medical Journal*, 1921, II, 152 ; and 1922, I, 791), namely, that the function of the parathyroid is chiefly to control the calcium mechanism of the body. These workers have shown that in practically all septic conditions there is a lowered calcium content of the blood (two types of deficiency are defined : one in which the total calcium is decreased, and one in which the active or ionised calcium is lessened without any marked alteration in the total amount), and once this can be restored, cell activity is stimulated and the condition gradually becomes normal.

The parathyroids appear to exercise a powerful influence on the nervous system, on the retention of an adequate amount of calcium in the tissues, and in neutralising toxic products of metabolism. It would seem that they are essential to life, since their total removal is followed by convulsions which end fatally. According to Dragstedt, writing in *The American Journal of Physiology*, November, 1923, animals whose parathyroids had been completely removed remained alive for at least one year if the diet contained a large amount of milk sugar. In pregnant animals, however, the lactose diet was ineffective, the animals dying of tetany, possibly because the poisonous substances were absorbed by the uterus. If parathyroidectomised dogs were fed for six weeks on milk-sugar diet and then on ordinary diet they remained healthy. It is suggested that possibly other organs (e.g., the liver) take up the functions of the parathyroids, and compensate for their absence. Without the administration of lactose partial removal of parathyroids sooner or later produces a condition of chronic tetany, and this also may be relieved by the ingestion of the gland substance.

Parathyroid Insufficiency.

An insufficiency of parathyroid secretion in the human subject is manifested by the development of muscular spasms and tremors. Some authorities hold that these symptoms are caused directly by the loss of calcium from the blood. Presumably the calcium acts as a sedative to the nerve endings, counteracting in a measure the efferent motor impulses there received. When the calcium sedation is normal, the muscle-nerve reactions are normal, but when the calcium sedation is diminished there ensues hyper-irritability; the faintest nerve impulse is exaggerated and interpreted as a positive stimulus to muscular movement. Noël Paton, on the other hand (*Edinburgh Medical Journal*, October, 1924), is of the opinion that a decrease in the calcium content of the blood is not the primary factor in the causation of the symptoms, but explains it as being due to methyl guanidine toxæmia. Whatever the explanation, there is apparently a parathyroid insufficiency which may be compensated by the administration of a reliable preparation of parathyroid glands derived from animals.

The detoxicating property of the parathyroid glands, also, renders the dried substance a very valuable therapeutic agent, though it is not clearly understood whether the action is direct or whether it is accomplished by stimulating certain tissues (e.g., the thyroid) to produce antitoxic substances.

Oliver Smith (*Lancet*, April 22, 1922, p. 796) states that while our knowledge of the physiology of parathyroid disease is imperfect, there are two effects that are constantly observed, viz., the occurrence of tetany and changes in calcium metabolism. There is a tendency to confound some of the milder cases with neurasthenia, and he believes

that many cases which he formerly considered to be Graves' disease were really parathyroid disease. He has observed the following four principal groups of symptoms characteristic of this condition: (1) tetany, (2) sensory changes, (3) myasthenia and (4) changes in the nails and hair.

In the majority of cases, says this writer, tetany does not occur, but merely a general excitability of the nervous system. Sensory changes are nearly always present; patients complain of ill-defined pains, usually attributing them to neuritis or rheumatism. Sensations of "pins and needles," and also a tired feeling in the muscles, are common. The nails lose their normal translucency and show an increased number of white spots. The hair tends to fall out.

Therapeutic Indications.

So many indications for the administration of parathyroid gland substance have been put forward that there is a danger of the remedy being regarded with scepticism and ignored even in those cases in which its exhibition has been followed by the most satisfactory results. In the following pages, only those cases are quoted that have been reported in the medical press or contributed by responsible authorities.

Grove and Vines have recorded important results from the administration of desiccated parathyroid substance in cases of **varicose, gastric and duodenal ulcers** (see *British Medical Journal*, 1921, II., 152, and 1922, I., 791). One tablet (1/10 gr.) was given each night and morning for the first four to seven days, then once daily whilst necessary. The effect of this medication was manifested at once, and reached its highest point in ten days, but the time required for complete healing varied with the extent of the ulcerative process. In some of the cases there was at first an exacerbation of the septic process, which suggests that parathyroid gland administration stimulates the natural defensive mechanism.

The authors point out that the majority of chronic diseases are due to protracted absorption of toxic substances from a septic focus, and that such absorption is accompanied by a decrease in the ionic calcium of the blood; they account for the beneficial effect of the parathyroid substance in the cases under review by the observed fact that in the blood of each patient, without exception, the ionised calcium was below normal, giving rise to irritation and ulceration. The administration of parathyroid raised the ionised calcium content to normal, and as a result the ulcers healed.

A physician reports that a lady of about 75 years of age, suffering from **pyloric ulcer**, with frequent attacks of vomiting, had been under treatment for more than a year without obtaining much relief, but when parathyroid gland was prescribed the symptoms disappeared

in about three weeks, and the lady now appears to be quite well. She was given 1/20 grain (3.2 mgm.) of desiccated parathyroid gland in Parke, Davis and Co.'s tablets, twice daily.

The value of parathyroid therapy in **sprue** has been demonstrated beyond question by Scott (*Transactions of the Royal Society of Tropical Medicine and Hygiene*, February, 1923, also *Lancet*, October 20, 1923). The author became impressed by the remarkable similarity existing between many of the symptoms of sprue and those occurring in other diseases in which calcium deficiency, or disordered calcium regulation by the parathyroid glands, plays a part, and he has had the opportunity of treating a number of cases of sprue of long duration, in which all the known forms of treatment had been adopted without the production of more than temporary benefit. Treatment with parathyroid and calcium has, however, been followed by the most striking results. "The cramps, the softness of the mouth, the acidity and flatulence rapidly disappeared, the stools regained their normal colour for the first time for nearly two years, and the patient steadily put on weight with marked improvement in the general state of health."

The author's theory is that "acute and chronic toxæmias react in some degree on the parathyroids, causing disturbance of calcium metabolism." Confirmation of the probable accuracy of this theory as to the etiology of the disease is forthcoming in a report on a case of sprue published in the *Journal of the Royal Naval Medical Service* (October, 1923, page 275), in which it is stated that the patient "some weeks before death had associated symptoms of tetany." The post mortem in this case appeared to indicate little abnormal condition of the organs, with one exception: "the thyroid was atrophied." No mention is made of the parathyroids, which, in any case, it would have been difficult to demonstrate post mortem. The classic symptom following parathyroidectomy is the onset of tetany, and the coincidence is very suggestive.

The *B.M.J.* (Dec. 15, 1923, p. 1135) contains an important article by Scott, in which are given analyses of the calcium content of the blood before and after treatment of sprue by parathyroid and calcium.

In all forms of chronic ulceration parathyroid would appear to be indicated. In **mucous colitis**, for example, we are informed that the administration of parathyroid is always worthy of trial. One prominent physician always prescribes calcium lactate in addition to parathyroid to commence with, omitting the calcium at an early stage of the treatment.

Another physician reports the case of a male, aged 45, who had been suffering from mucous colitis for 15 years. Parathyroid, 1/20 grain (3.2 mgm.), was administered twice daily for six weeks, and at

the end of this time the general and local conditions were much improved. Symptoms practically disappeared although the patient required to take parathyroid at intervals to maintain the improvement.

Amœbic dysentery has also yielded to parathyroid and calcium treatment after emetine had failed to produce a definite cure.

Grove and Vines have also obtained favourable results from parathyroid administration in **suppurative processes of the nose, throat and ear**. They attribute to the gland a more or less specific action on calcium metabolism, combined with or resulting in a generalised stimulation of metabolism as a whole. They consider that its administration provides the tissue cells with the most favourable conditions for disease resistance.

The medical officer of an isolation hospital, writing to *The Lancet* of February 17, 1923 (p. 359), states that a great amount of expense and trouble having been caused by delay in evacuating scarlet fever cases owing to the persistence of **nasal and aural discharges**, he had endeavoured to obviate the occurrence of such sequelæ by the administration of parathyroid gland. This plan appears to have been successful in a small number of cases, as in only one did a discharge appear.

Chorea and other conditions characterised by muscular twitching and spasmodic contractions have been treated, frequently with decided benefit, by the administration of parathyroid substance.

In children, chorea is almost invariably associated with acute rheumatism. As already pointed out, one function of parathyroid is to control the calcium mechanism of the body, and in many septic processes there is a diminution in the ionic calcium content of the blood. It may be that in certain forms of chorea sepsis is the cause of the trouble, in which case it is not difficult to understand why parathyroid is often useful. Various authorities have demonstrated small cortical lesions with the presence of rheumatic diplococci, which might be consistent with a possible septic basis.

In at least one large hospital in England parathyroid gland medication has been employed in chorea with marked success. It is important, however, in the case of children, to commence with a small dose, 1/20 grain (3.2 mgm.) once daily being sufficient in most cases.

Certain forms of **epilepsy** are due to the absence or insufficiency of calcium in the blood, whereby cerebral irritation is set up. Here, too, the indication is for parathyroid substance and a calcium salt, but other glands may often be added to the prescription with advantage. In children it is advisable to add thymus gland substance, because that gland is largely concerned in the child's nutrition, and in nearly all these cases a nutritional uplift is needed. If the case presents evidence of toxæmia, especially such as would be produced by foci

of infection in the nose, throat or accessory sinuses, the addition of 1/10 grain (6.5 mgm.) of dried thyroid gland to the parathyroid-calcium combination is likely to be advantageous—if there are obvious signs of hypothyroidism a larger dose of thyroid would be called for. If the epilepsy develops at puberty, or at the menopause, or during any period in which there is a special strain, it is advisable to add ovarian or orchic substance in doses of 10 grains (0.65 gm.) per diem.

In **paralysis agitans**, which is probably caused by sclerotic changes in the parathyroid glands developing with age, one tablet may be given twice a day. Benefit may not be observed for weeks or even months, but perseverance with the use of a *genuine* preparation will generally be rewarded. It is sometimes advantageous in this and in other conditions of parathyroid insufficiency to administer fairly large doses of one of the calcium salts (the chloride, iodide or lactate) simultaneously with the gland substance.

Berkeley, of New York, reported in *The Medical Record* of July 5, 1916, that though parathyroid treatment does not appear to be invariably successful in cases of paralysis agitans, yet from 60 to 70 per cent. of sufferers from that complaint who have given the remedy a fair trial for from three to six months have been greatly benefited, the progress of the disease being apparently arrested, or at least greatly retarded.

Scott (*Practitioner*, November, 1917, p. 479) states that parathyroid treatment is well worth trying in **paralysis agitans**. Having used it in a few cases, he has found that it considerably modifies the trembling, and that patients feel the better for it. A correspondent of the *British Medical Journal* (1922, I., 744) states that in some cases of paralysis agitans, parathyroid tablets, 1/10 grain, thrice daily, do great good.

A writer in *The Practitioner*, July, 1924, favours the use of hyoscine in combination with parathyroid in cases of this kind. In his experience post-encephalitic cases show much less resistance to treatment than those of the senile type. In his opinion parathyroid therapy definitely exercises a beneficial control upon the tremor as well as upon the patient's general comfort and sense of well-being.

Accidental injury or extirpation of the glands during operations on the thyroid is a frequent cause of parathyroid insufficiency. The development of **tetany** after such an operation may be taken as an indication that one or more of the parathyroids have been removed or injured. In such an event the administration of Parathyroid and Calcium Tablets should prove beneficial.

Hertz reports in *The British Medical Journal* of February 6, 1915, (p. 246), a case of **restlessness and tremor** following the removal of a parenchymatous goitre. The patient had an enormous appetite, yet lost weight rapidly. Thyroid administration made matters worse.

After some months of ineffectual use of various remedies, parathyroid gland was administered, 1/10 grain four times daily. Weight was rapidly gained, all the symptoms disappeared, and in a month the man was well. The gland administration was continued, however, for some two years.

(In the light of present knowledge the above dose would appear to be excessive. It is generally considered that, in an ordinary case, the daily dose should not exceed 1/10 grain and, in some instances, this dose may be still further reduced. See section on Dosage, p. 138)

In the *Glasgow Medical Journal* for October, 1920 (also *British Medical Journal*, 1920, I., 501), two cases are reported of an infantile disorder characterised by idiocy, depression, fibrillary twitchings in the muscles, jerking movements of the limbs, convulsions and inability to balance. As these symptoms were thought to resemble those produced in animals by removal of the parathyroid glands, imperfect function of those organs was suspected and parathyroid gland tablets were administered. In both cases marked improvement resulted. The author says: "It is uncertain how long treatment with parathyroid gland substance should be continued, but judging from the first case, a state of health is reached when it is no longer required. In the second case, the gland substance was discontinued twice, and on both occasions the child was not so well, but recovered on administration being resumed."

Massaglia, writing in *Endocrinology* (May, 1921), reports some important animal experiments which show unmistakably the similarity between the effects of parathyroid insufficiency and the symptoms of **eclampsia** in the pregnant woman. He showed that the removal of three parathyroids (leaving one *in situ*) does not impair health, but eclampsia is likely to supervene if pregnancy occurs; that the first intimation of eclampsia in the animal is a slight albuminuria; that among the early symptoms is a tendency toward tetanic movements; that the relative amount and contents of the urine of the animal were identical with those of the eclamptic woman; that the proportion of fatalities was the same in both; that damage to liver and kidneys was the same in both; that meat diet favoured the onset in both, while milk (rich in calcium) seemed preventive and curative; that treatment with calcium and parathyroid gave uniformly good results.

We are informed that parathyroid is worthy of trial in **hyperemesis gravidarum**. In two cases reported, parathyroid relieved the condition after a short time—four hours in one case and two hours and forty minutes in the other.

Several conditions which have been classed under the heading Vasomotor Neuroses have been found to be amenable to parathyroid and calcium treatment. Amongst these are **Raynaud's disease**, which

is regarded as an expression of vaso-constrictor spasm, and **erythromelalgia**, as the result of vaso-constrictor paralysis. **Angio-neurotic oedema** is another condition involving a disturbance of vaso-motor innervation. It is not surprising to learn, therefore, that parathyroid has been administered in cases of this kind with most encouraging results. Much more common is **erythema pernio** (chilblains) the etiology of which appears to be similar, though it is sometimes regarded as a simple dermatitis. In all of these conditions variations of capillary permeability and tone are observed, and though vaso-dilator impulses play a part in their production it is possible that decalcification of the blood may be in some degree responsible, and cases both of Raynaud's disease and of chilblains are known to have responded rapidly to parathyroid and calcium treatment. In some of these the urine is so loaded with calcium oxalate as to become quite solid on cooling. It is suggested, and indeed in at least one case it is believed to have been proved, that the cause of the trouble was excessive ingestion of sugar. Through an inverted metabolism the sugar may be split up *in vivo*, just as it can be chemically *in vitro*, with the formation of oxalic acid. This seizes on, and removes the calcium from the blood, the latter permeating the tissues more freely in consequence, and producing in the extremities, where the circulation is slower, an oedematous condition, which is especially liable to frost-bite. The case referred to cleared up in a week on 30 grains of calcium lactate daily and stoppage of sugar.

Children and old people are often subject to chilblains, particularly when the circulation is sluggish. The dose for young people is one parathyroid and calcium tablet, and for adults two to four tablets, daily, for a week or ten days, repeating the course if necessary after a week's intermission.

Osteomalacia and other conditions showing calcium impoverishment are indications for parathyroid-calcium medication.

An interesting report reaches us concerning the use of parathyroid in the treatment of forty dogs suffering from an advanced type of osteomalacia. The animals were from one kennel, and it is interesting to note that there had been much in-breeding extending over a period of some years. The clinical picture suggested a condition closely resembling that of acute rheumatoid arthritis. The animals moved with difficulty and were obviously in pain. The bony structures were remarkably soft, especially the parietal bones, and in some instances the nasal bones were so mobile that it was quite an easy matter to twist the structures several degrees out of the normal. All the dogs were given small doses of parathyroid together with anterior lobe pituitary, the object of the latter being to fix the calcium. In three months the animals had made a remarkable improvement, in fact, the majority showed no evidence whatsoever of osteomalacia.

The writer of an article in *The Practitioner* for May, 1918 (p. 442), says that the original cause of **hyperthyroidism (Graves' disease)** probably acts as a disturber of all the internal glands, particularly the thyroid and the parathyroid, and that treatment by appropriate glandular preparations is a most important auxiliary to medical or surgical measures directed against causative factors such as intestinal, uterine, oral or nasal infection. In most cases, the author says, there is evidence of thyroid and suprarenal excess, but the nerve tremors point to parathyroid deficiency, and administration of the gland is often beneficial in this respect. In cases which show continued low blood pressure, combined suprarenal and parathyroid administration is often very effective.

Another author, writing in *The Practitioner*, July, 1924, also claims to have treated eleven cases of Graves' disease with distinct improvement in every case. The tremor, nervousness and tachycardia in particular showed material benefit, whilst in five cases there was also a reduction in the proptosis, and in goitre.

A case of severe **paroxysmal tachycardia** over which no drug or dietetic treatment exerted the least control, and in which a speedy fatal termination seemed inevitable, is reported in *The Lancet* of October 21, 1922. At the beginning of 1922 the attacks, which completely disabled the patient, averaged three per week, and between the attacks the patient could not rise from a chair, or walk from one room to another, or turn over in bed, without an alarming acceleration of the pulse. On administration of Parke, Davis & Co.'s Parathyroid Gland Tablets, 1/10 grain (6.5 mgm.) three times a day, improvement was quickly evident. The author of this report refers to a similar case recorded in *The British Medical Journal* of December 10, 1921 (p. 987), and suggests that the antitoxic function of the parathyroids favourably influences muscular tone, in which beneficial effect the heart participates.

A writer in *The British Medical Journal* of June 24, 1922 (p. 1012), states that parathyroid gland substance is a useful adjunct to other measures outlined by him in the treatment of **psoriasis**, and suggests that one of Parke, Davis & Co.'s 1/10 grain tablets be administered twice daily.

The value of parathyroid in this condition has been emphasised by other workers and we have received reports which seem to demonstrate its possibilities in this condition.

In a paper submitted to the Section of Therapeutics and Pharmacology of the Royal Society of Medicine (reported in the Proceedings, Vol. XVI., 1923, pp. 18-22), Grove referred to numerous other conditions which had proved to be amenable to parathyroid treatment. These include the rheumatic group which "showed

invariable calcium deficiency"—**rheumatoid arthritis, osteo-arthritis, chronic rheumatism and sciatica.** "In every case there was undoubted improvement after the administration of parathyroid." **Urticaria, eczema and chlorosis** were also reported to have improved under parathyroid treatment.

Preparations of Parathyroid.

For use in medicine, the parathyroid glands of cattle are dissected out in the abattoirs by a specially trained operative, and every batch is inspected both macroscopically and microscopically by a competent pathologist. A casual observer would find it almost impossible to distinguish between parathyroids and cervical lymph glands or similar tissues, hence it is quite possible that conflicting reports of successes and failures from parathyroid administration may be accounted for by the varying qualities of the preparations used.

The precautions taken by Parke, Davis & Co. enable them to guarantee that a high percentage of the desiccated substance used in their tablets is genuine parathyroid tissue, and therefore, physicians who prescribe **Parathyroid Gland Tablets (P., D. & Co.)** have every assurance of employing a remedy possessing full physiological activity. Each tablet contains either 1/10 grain (6.5 mgm.) or 1/20 grain (3.2 mgm.) of the dried gland.

DOSAGE.

The usual dose of parathyroid is 1/10 grain once or twice a day, and in the majority of cases this is sufficient. In their original work Grove and Vines used 1/10 grain of the desiccated gland daily, and no advantage appeared to them to be gained by increasing the dose to 1/5 grain. Some prefer to prescribe a tablet containing 1/20 grain twice a day. This may be continued for a week or possibly a fortnight, and then dropped to 1/20 grain once a day. Subsequently this amount may be given every other day for as long as is thought necessary. It is generally an advantage for the first few days of treatment to give in addition 10 grains (0.6 gm.) of calcium lactate thrice daily.

Continued administration of parathyroid gland in doses much in excess of the amount recommended has given rise to undesirable symptoms. Thus, one observer has reported nervousness and insomnia during parathyroid treatment, while in another instance the patient is said to have developed a psychosis, which was alleviated when the parathyroid was discontinued. On the whole, however, over-dosage in connection with parathyroid therapy has thus far been found to be a relatively rare occurrence even when the gland is taken over a long period of time. As with all other therapeutic substances the correct dose is that amount which will produce a physiological effect.

According to one observer the parathyroid is best given before food, the view he takes being that the moment of most intense internal secretion on the part of the parathyroid and thyroid is immediately before food; consequently, he always administers these gland products twenty to thirty minutes *ante cibos*, and the results appear to justify the method.

Parathyroid and Calcium Tablets (P., D. & Co.) contain Desiccated Parathyroid Gland, 1/40 grain (1.6 mgm.), Calcium Lactate, 5 grains (0.325 gm.).

In cases of pronounced osteomalacia and other conditions in which there is obvious disturbance of the calcium metabolism it is advantageous to have a compound tablet in which the (presumably) deficient gland is associated with calcium lactate. The dose of parathyroid is kept low in order to allow continued administration with (or without) intermission over such a period as may be indicated. For children, in cases of parathyroid deficiency, one tablet may be crushed to powder and administered daily with sugar and water. Adolescents and adults may take two to four tablets daily for 8 or 10 days, thereafter reducing the dosage, or intermitting treatment for a week if considered advisable.

In addition to the foregoing, parathyroid gland substance is one of the ingredients in **Tetraglandular Tablets (P., D. & Co.)** which are of service in conditions in which parathyroid insufficiency is associated with incompetence in other members of the glandular system. Each of these tablets contains Desiccated Parathyroid Gland, 1/40 grain (1.6 mgm.), Desiccated Thyroid Gland, 1/3 grain (0.02 gm.), Desiccated Suprarenal Gland, 3/4 grain (0.05 gm.), Desiccated Pituitary Gland, 1/3 grain (0.02 gm.). The dose is 1 or 2 tablets three times daily.

P., D. & Co.'s. Parathyroids are Genuine.

Recently, fifty-three specimens of parathyroid tissue taken at random from a batch of material, prior to desiccation were submitted to a prominent West End surgeon who, in turn, handed them to a well-known pathologist. The report showed that nineteen of the specimens consisted solely of parathyroid tissue. In thirty-three, so-called thymic or lymphocytic tissue was visible under the microscope; one section only was devoid of parathyroid. In the fifty-three representative sections examined, the lymphocytic tissue amounted to approximately 10 per cent. Owing to the intimate association of this tissue with the parathyroid, it is impossible to exclude it entirely. In no instance was there any thyroid tissue.

THE SUPRARENALS.

The suprarenal glands are to be regarded as amongst the most important members of the endocrine system. They consist of two triangular-shaped bodies, one surmounting each kidney after the fashion of a helmet. For practical clinical purposes, and also histologically, the glands are divided into two parts, an outer or cortical portion, and an inner or medullary portion. The medulla is an outgrowth of the sympathetic nervous system and its abnormalities chiefly affect that system. The cortex, on the other hand, is developed from the Wolffian body, which also provides the interstitial cells of the reproductive organs, and its abnormalities take effect in the reproductive system, an example of which is seen in the premature sexual development that often attends tumours of the suprarenal cortex.

The active principle of the secretion of the medulla is the well-known Adrenalin. The secretion of the cortex has not been isolated and, therefore, when it is desired to administer preparations containing the cortex, desiccated suprarenal gland should be prescribed.

The important functions of the suprarenal gland are to assist in sexual development, especially in early life; to maintain muscular tone—this includes the arterial muscles, especially those supplied by the sympathetic—and, therefore, maintenance of arterial tension; and to protect the individual against bacterial infection. The glands increase carbohydrate metabolism, destroy toxins produced by muscular activity, and decrease fatigue. Under-functioning of the adrenals is responsible for Addison's disease, while over-functioning leads to hyperpiesis and is held by some to be a factor in such conditions as arteriosclerosis, nephritis and certain forms of diabetes mellitus. Others, however, maintain that increased secretion of the suprarenal gland is not generally attended by phenomena that may be called pathological, and assert that the only abnormal development, if any, is a precocious sexuality.

A plentiful supply of suprarenal secretion ordinarily means that the individual has a vigorous muscular and nervous constitution, is one who forges ahead in all pursuits he undertakes, is capable of much mental concentration, and can withstand unusual mental and physical shocks. Deficient secretion, on the other hand, is characterised chiefly by muscular weakness and loss of general body tone. This is manifested in fatigue (physical or mental), heart weakness, low blood-pressure, cold hands and feet, and other evidences of defective circulation. Atony of the musculature of the alimentary canal is also likely to be present, and, consequently, indigestion and intestinal stasis. The toxæmia arising from the latter makes further demands upon the glands, and thus a vicious circle is completed. Suprarenal insufficiency also gives rise to various forms of neurasthenia, and these are sometimes benefited by administration of the gland substance.

The suprarenal plays an important part in ridding the body of bacterial toxins, and it is well-nigh depleted during the course and convalescence of nearly every infectious disease. Depletion of the suprarenal glands may also be caused by emotional experiences—fear, rage, pain, mental shock, continued worry, etc. Extreme manifestations of lack of suprarenal secretion are seen in Addison's disease, in which the suprarenal glands are almost totally destroyed.

Deficiency in natural secretion may be more or less successfully compensated for by the administration of the glandular substance, but at the same time all forms of toxæmia—infective, putrefactive, etc.—must be counteracted, alkaline mineral salts administered to replace those that are lacking in the system, and any defect in function of the other glands of the body remedied by the administration of the corresponding glandular principle or extract.

Suprarenal Therapy.

For medicinal purposes the glands obtained from healthy animals, either the sheep or ox, are carefully trimmed, dried, reduced to powder and physiologically tested, one part of the dried gland representing five parts of the fresh gland.

The general indication for the administration of desiccated suprarenal gland is **hypoadrenia**. The drug is best given in doses of two to four grains (0.13 to 0.26 gm.) three times a day.

Some authorities consider that most cases of **neurasthenia** are the result of adrenal insufficiency. Certainly, emotional shocks deplete the adrenals and lead to fatigue, asthenia and lack of energy. In cases of this kind, tonics containing strychnine which tend to stimulate the suprarenals to increased function appear to be contra-indicated, since these organs are already worn out. Thyroid, in addition to suprarenal, often helps to stimulate cellular activity. In all probability Adrenalin would give more rapid and decisive results, but it is not possible to use Adrenalin in any condition in which it is likely to be needed for a protracted period because, to be effective, it must be given by hypodermic injection; moreover, its effect is evanescent.

Desiccated suprarenal (whole) gland has also been used with good effect as an adjuvant to ovarian substance and desiccated thyroid in certain cases of **sexual infantilism**. In various other conditions arising from disturbed hormone balance, the administration of suprarenal gland, in combination with other gland substances, according to the indications, appears to be valuable. Some authorities hold that the influence of adrenal secretion is not due entirely to Adrenalin, and it is claimed that results have been obtained from the administration of dried (whole) suprarenal which were not given by Adrenalin alone.

Adrenalin* Therapy.

While the suprarenal gland is largely employed by endocrinologists, especially in combination with other gland products, its use has, to a certain extent, been overshadowed by the fact that it is from this gland that we obtain the definite active principle—Adrenalin—the indications for the administration of which are clearly defined. Adrenalin owes its therapeutic value to the fact that when given hypodermically it quickly stimulates the junctions of the sympathetic nerves with the muscles which they supply. The most pronounced effect of its administration, therefore, is a contraction of the peripheral arterioles and a rise in blood pressure. It is a most valuable remedy in the treatment of **surgical shock**. The approved method of administration in cases of this kind is in a saline intravenous infusion. In cases marked by profound and dangerous shock or collapse this method may prove too slow, or ineffective; recourse should then be had to the procedure described by Crile and termed centripetal arterial transfusion. Briefly, this consists in the insertion into an artery of a canula directed toward the heart. Into the rubber tubing which is attached to the canula, 15 to 30 minims (1 to 2 c.c.) of 1 : 1,000 Adrenalin Solution are injected as soon as the saline infusion begins. The effect of this is to bring the Adrenalin immediately into contact with the larger arteries and the heart. This is an important point, because it is argued that in the intravenous administration of Adrenalin the drug comes into contact first with those structures that have the least important part to play in the elevation of the blood pressure. By bringing Adrenalin into immediate contact with the larger arteries and the heart, precious time is saved. Sometimes, even in apparent death, the heart will resume its contractions. Several cases have been reported where Adrenalin in doses of 0.5 to 1 c.c. has been injected directly into the ventricle of the heart, in some instances with excellent results.

Adrenalin is useful in the treatment of **hæmorrhage** owing to its ability to contract the lumen of the blood-vessel at the bleeding point, thus favouring formation of a clot. In severe hæmorrhage one drachm (3.5 c.c.) of Adrenalin Solution in 16 ounces (455 c.c.) of hot normal saline solution may be given by hypodermoclysis in the subcutaneous tissue under the breast, or by infusion directly into a vein. Superficial hæmorrhages and others which, because of their location, are readily accessible, may be treated by the topical application of previously moistened compresses to which are added a few drops of 1 : 1,000 Adrenalin Solution. Among the hæmorrhages which are amenable to this local treatment are those from the nose, mouth, throat, ear, vagina, uterus and rectum. In **hæmatemesis** one drachm (3.5 c.c.) of the 1 : 1,000 solution may be given orally. In **hæmaturia** the

* The word "Adrenalin" was first applied to the blood-pressure-raising principle of the suprarenal gland isolated by Takamine in 1900, and introduced to the medical profession by Parke, Davis & Co. in 1901.

injection into the bladder of an ounce (28·5 c.c.) of 1 : 5,000 or 1 : 10,000 solution of Adrenalin is frequently effective.

Because of its vaso-constrictor action, Adrenalin is utilised, in the form of a compress or spray, as an application to mucous membranes which are the sites of **vascular engorgement** or inflammation. A dilution of 1 : 5,000 or 1 : 10,000 is customary when Adrenalin is used for this purpose.

Adrenalin is also effective as a hæmostatic because it shortens the coagulation time of the blood; this action has been demonstrated by Cannon and his co-workers to be particularly evident when small doses are injected intravenously or even subcutaneously.

It is a valuable addition to local anæsthetics because it bleaches the operative area, giving the surgeon a clear field, and it confines the effect of the local anæsthetic to the area into which it is injected, thus prolonging and intensifying the anæsthesia.

In the paroxysm of **asthma** it acts in a striking manner, because of its effect on the bronchioles. Four to eight minims (0·25 to 0·5 c.c.) of the 1 : 1,000 solution injected hypodermically will, in the majority of cases, bring almost instantaneous relief; but when a patient does not readily respond to the administration of Adrenalin, this medicament should not be pushed. Some practitioners have noticed that the injection of Pituitrin in combination with Adrenalin enhances and prolongs the action of the latter. The Pituitrin effect is especially desirable in cases giving evidence of cardiac embarrassment.

By the endocrinologist, Adrenalin is regarded as a synergist to posterior pituitary secretion and, in some respects, to the hormone of the thyroid gland. It appears to be a direct antagonist to pancreatic secretion, especially with respect to its function in carbohydrate metabolism.

On the whole, the active principle of the medullary portion of the suprarenal gland—Adrenalin—is sparingly used in organotherapy. The reason for this is that the action of Adrenalin is immediate and transient, whereas a more sustained effect is obtainable by the administration of the desiccated suprarenal gland. Adrenalin, however, occupies an important place in clinical endocrinology as an aid in the diagnosis of certain functional changes in some of the ductless glands.

DOSAGE.

For oral administration, the 1 in 1,000 Adrenalin Chloride Solution may be given in doses of from 5 to 30 minims (0·3 to 2 c.c.); when a pronounced effect upon remote organs is required the dose must be repeated at brief intervals. For hypodermic injection, from 2 to 15 minims (0·12 to 1 c.c.) of the 1 in 1,000 solution, preferably diluted with normal saline solution. For intravenous injection, from 2 to 5

minims (0.12 to 0.3 c.c.) of the 1 in 1,000 solution diluted with at least 20 (preferably with 100) times the amount of warm normal saline solution, and introduced slowly.

TOPICAL USES.

The 1 in 1,000 solution may be employed in epistaxis, bleeding gums or tooth sockets, or small wounds. In the treatment of inflamed mucous membrane of the throat, nasal passages, urethra or vagina, also of vesical or urethral hæmorrhage, it is best to dilute the 1 in 1,000 solution with from 2 to 10 volumes of normal saline solution. For the throat and nose an oily solution is often preferable to an aqueous one, and is available in Adrenalin Inhalant. For rectal use, Adrenalin Suppositories (four varieties) are prepared. Adrenalin Ointment (two varieties) is applicable in eye, nose, and rectal affections. Adrenalin Throat Lozenges contain the medicament in conjunction with sedative and expectorant agents agreeably flavoured.

Adrenalin as a Diagnostic Agent.

Adrenalin may be employed as a diagnostic agent in suspected hyperthyroidism. The test is known as the Goetsch test, named after Professor Goetsch, who first described it. It is based on the fact that thyroid secretion sensitizes the body cells to the action of Adrenalin. The test is carried out by injecting about 0.5 c.c. of the 1 : 1,000 solution and then observing the changes in the subjective symptoms of the patient and the characteristic blood-pressure curve. Blood-pressure readings are taken over a period of 10 hours at intervals varying from $2\frac{1}{2}$ minutes at the beginning of the reaction to 10 minutes at the end. In positive cases the systolic blood pressure rises at least ten points during the first fifteen minutes, with an accompanying increase of about ten beats per minute in the pulse rate. Soon there is noted a slight fall in systolic pressure and then a secondary rise. In about ninety minutes the blood pressure is back to normal. The subjective symptoms are sometimes striking. There are heart consciousness, apprehension, marked tremor and pallor, which is occasionally followed by flushing and sweating. The greatest diagnostic importance of the Goetsch test is in distinguishing cases of mild hyperthyroidism from those of incipient tuberculosis.

A satisfactory test for suprarenal function can be performed by first examining the blood for sugar, and then injecting subcutaneously fifteen to twenty minims (1 c.c. to 1.25 c.c.) of 1 : 1,000 Adrenalin Chloride Solution. In cases of suprarenal irritability there is an increase in blood sugar which comes on in about thirty minutes and lasts for several hours. A transient glycosuria may likewise be noted.

Loewi's test for pancreatic diabetes is dependent upon the fact that the suprarenal glands and the pancreas are physiological antagonists. In pancreatic diabetes there is impairment if not destruction of some of the secretory cells, which allows certain Adrenalin effects to be more

pronounced. One or two drops of 1 : 1,000 Adrenalin Chloride Solution should be instilled into one eye. In positive cases—cases of pancreatic insufficiency—there will be a prompt dilatation of the pupil.

Suprarenal Compound Tablets.—These tablets contain desiccated suprarenal gland, pituitary substance and thyroid gland—one grain (0.065 gm.) of both the first and second, and half-grain (0.032 gm.) of the third ingredient. This combination represents the glands that control the kinetic drive of the body and are concerned in the maintenance of normal metabolism. Its administration is indicated when the symptoms point to hypofunction of the glands represented. The dose to be given will be governed by the patient's tolerance for thyroid medication.

Tetraglandular Tablets.—These tablets contain the same gland substances as the preceding, though in different proportions, with the addition of parathyroid, which enlarges their scope.

The administration of suprarenal gland in association with orchic substance and the anterior lobe of the pituitary gland is of value in certain conditions arising from hypofunction of those glands, in which cases Orchic Compound Tablets (see note on page 167) may meet the indications. The combination of the suprarenal and pituitary glands with ovarian substance, as provided in Ovarian Compound Tablets, has a special field of usefulness (see note on page 161). See also Thyrafer Tablets (p. 126), and Thyrovarian Compound Tablets (p. 161).

THE PITUITARY.

The pituitary body, or hypophysis as it is sometimes called, is a small gland about 1 cm. in diameter, situated at the base of the brain in the *sella turcica*, or pituitary fossa of the sphenoid bone. It is connected with the brain by a prolongation from the floor of the third ventricle, known as the infundibulum.

Anatomically the pituitary body is described as consisting of an anterior and a posterior lobe, of which the former constitutes about two-thirds of the gland and is made up of what is termed the pars anterior and the pars intermedia, separated from each other by a cleft. In spite of the fact that the pars intermedia, in common with the pars anterior, arises from the ectoderm of the primitive buccal cavity, it is usually classed by histologists with the posterior lobe which develops from the floor of the third ventricle of the brain, presumably because the pars intermedia is in close contact with this lobe and almost inseparable from it.

Experiment has shown that removal of the anterior lobe is followed by death in a few days, although if only a portion of the lobe is excised the animal will probably survive, but will exhibit the usual symptoms of anterior lobe insufficiency. Removal of the posterior lobe is not necessarily fatal.

In a consideration of the functions of the pituitary body, and for practical therapeutic purposes, the gland may be considered as consisting of an anterior and a posterior portion, the latter including the *pars intermedia*.

Histologically the structure of the two lobes is quite different, and their physiological functions are also quite distinct, as will be apparent from the following brief outline.

The Anterior Lobe.—The anterior lobe of the gland promotes skeletal growth and stimulates sexual development, especially in the male. Anterior lobe insufficiency produces varying degrees of smallness of stature, associated usually with sexual infantilism. The anomalies of skeletal growth, however, will depend entirely upon the period of life in which the function of the anterior lobe becomes impaired. If it occurs in adult life when the individual has already attained his full growth, and ossification of the epiphyseal ends of the long bones has taken place, the retrogression of the anterior lobe will of course not be attended by changes in stature. In such adult cases usually the only evidence of anterior lobe insufficiency is a sudden loss of libido.

Increased secretion of the anterior lobe, when carried to extreme degrees, results in gigantism in pre-adolescent patients and in acromegaly in adults. Here again the ossification of the epiphyseal ends determines whether the hypersecretion will result in gigantism or not. In an adult, of course, gigantism cannot develop. The increased anterior lobe secretion makes its presence felt by increasing the thickness and, in general, distorting the shape of the short and flat bones. Hence we have in acromegaly the characteristic broad wrist and palm, the massive lower jaw, and the excessive prominence of the nasal bones resulting in prognathism.

The Posterior Lobe.—The important functions of the posterior lobe are stimulation of non-striated muscle fibre, participation in carbohydrate metabolism, and assistance in sexual development, especially in the female. Deficiency in posterior lobe secretion causes muscular atony, proceeding in extreme cases to muscle dystrophy, and a slowing up of the carbohydrate metabolism, with an enormously increased sugar tolerance. The increase in sugar tolerance is accompanied by a craving for carbohydrate food, and the imperfect combustion and elimination of the excessive amount of carbohydrates which these patients consume causes a characteristic form of obesity. It is known as girdle obesity because of its predilection for the lower part of the trunk between the umbilicus and the symphysis pubis.

In cases in which both the anterior and the posterior lobe are deficient, the clinical picture is a composite of the sexual infantilism of the anterior lobe and the girdle obesity of the posterior lobe. It is known as the Fröhlich type of adipose genital dystrophy.

If either hyposecretion or hypersecretion of any part or all of the posterior lobe is accompanied by enlargement of the gland, there will be found, in addition to the classical symptoms, certain signs produced by the pressure of the enlarged gland upon the brain. The symptoms will vary with the direction in which the pressure is exerted, but invariably in these cases headache is a pronounced symptom. The patient describes the pain as being in the centre of the cranial cavity or directly at the back of the eyes. Frequently in connection with menstruation, and occasionally during pregnancy, there is a temporary enlargement of the pituitary gland, with the development of pituitary headache.

Discrimination in Pituitary Therapy.—As a consequence of the wide difference in function of the two portions of the gland, and in the symptoms arising from insufficiency of either the whole gland or one or other of its parts, discrimination is necessary in the application of pituitary therapy, and selection should be made according to the indications of the case from the three varieties of pituitary preparations available for therapeutic use, namely : those derived from the anterior lobe ; those from the posterior lobe ; and those from the whole gland.

Anterior Lobe Therapy.

Disorders of the anterior lobe have been tentatively classified by Engelbach (*Endocrinology*, 1920, Vol. IV, No. 3) according to whether they are the result of hypoactivity or hyperactivity of the gland. Each of these general classes is divided into **pre-adolescent and post-adolescent diseases**, depending upon the relationship which they bear to puberty and to the occurrence of the epiphyseal fixation of adult life. Further qualification with regard to tumour as a cause is made by use of the terms aneoplastic and neoplastic.

When a deficiency of secretion occurs in the pre-adolescent period of life the patient manifests symptoms of the Lorain-Levi type. This type displays a classical arrest of growth in the osseous system, with complete aplasia of the genital system, without any endocrine symptoms referable to the posterior lobe.

Under post-adolescent hyposecretion may be classed many cases of amenorrhœa, dysmenorrhœa and metrorrhagia, which are to be differentiated from similar cases of other causation by their response to anterior lobe treatment. To belong in this classification these cases should show no posterior lobe complications.

Two distinct disorders are recognized as the result of hyperactivity of the anterior lobe—gigantism and acromegaly—beginning respectively in the pre-adolescent and post-adolescent periods of life. These should be uncomplicated, for when combined with polyuria, increased metabolism, adiposity, decreased sugar tolerance, or unstriated muscle contractions, resulting from posterior pituitary disease, the syndrome should be classed with bilobar disorders.

A typical case of the **Lorain-Levi type** is to be distinguished from cases of adipose genital dystrophy (Fröhlich's syndrome) by the absence of girdle obesity, in which the deposit of fat extends, with occasional variations, from the lower part of the abdomen to the lower third of the thigh. Other symptoms of posterior lobe insufficiency, as polyuria, increase in sugar tolerance, etc., are also absent. From the foregoing it will be seen that to be properly classed as a typical case of the Lorain-Levi type, only signs and symptoms that indicate anterior lobe involvement, without appreciable defect in the posterior lobe should be present. The patient is short of stature, due to a deficiency in the growth of the long bones. The genitalia remain infantile in development, and secondary sex characteristics are absent. Frequently the only complaint of the female patient is amenorrhœa, while at other times intense headache is complained of.

In these patients administration of anterior lobe is indicated to supply the lacking secretion. As a rule the earlier treatment is given the better will be the result.

Amenorrhœa, dysmenorrhœa, or metrorrhagia may occur as a result of relative or absolute anterior lobe insufficiency. In many cases, perhaps all, there is a secondary deficiency on the part of the gonads which usually show a slight tendency toward underdevelopment. In determining the etiology, the possibility of pelvic disease or other etiological factor must be taken into account. In doubtful cases the therapeutic test may be applied by the administration of one of the anterior lobe preparations. In treatment these should be supplemented by the administration of a preparation of any other gland that appears to be defective.

The occurrence of **gigantism** and **acromegaly** as a result of over-secretion of the pituitary anterior lobe depends upon the relationship borne by the oversecretion to ossification of the epiphyses. If it occurs before this has taken place, the overgrowth will be in the length of the bones, resulting in gigantism; while if ossification has taken place and the long bones are no longer capable of axial increase, overgrowth will result in a broadening of these bones, with a general enlargement of such bones as the frontal, the upper and lower maxillæ, etc.

In gigantism, heredity is probably an etiological factor, although acute infections, trauma, and the normal physiological changes of puberty and pregnancy have been given as causes for some of these cases. A case has been reported in which sudden and unusual growth began after an attack of typhoid fever. Occasionally there occurs a coincident hyperplasia of the genital system.

In acromegaly, the face assumes a rather characteristic appearance owing to an increase in size of the malar bones, the inferior maxilla, and the frontal bone, especially in the superciliary ridges. The hands become flat and spade-like, with broad, thick fingers, clubbed at the ends. The nose, lips, and feet become permanently enlarged.

Among the early subjective symptoms are headache, pain in the face, and paræsthesias in the head and face. Females seem to take on certain male characteristics, and men patients find their masculinity accentuated. A feeling of increased strength is followed by lassitude and weakness.

In gigantism and acromegaly, *per se*, there is no indication for the administration of anterior lobe preparations, except in those cases in which the primary oversecretion of the gland has been followed by a gland deficiency, on account of which the patient is manifesting characteristic symptoms.

Theoretically, the anterior lobe ought to be of value in **functional sexual impotence**, and at least one well-known clinician has reported beneficial results from its use in this condition. On an entirely empirical basis the anterior lobe has been used in the treatment of **asthma**. It is usually given in combination with desiccated suprarenal in the proportions of one grain of anterior lobe to two grains of the suprarenal preparation, three times a day. Although the action of the anterior lobe in these cases has not yet been explained, there can be no question as to its beneficial nature.

DOSAGE.

Anterior lobe has been prescribed by different clinicians in doses of from 1 to 50 grains a day. This wide latitude is necessary on account of the fact that the ideal dose would naturally be that amount which most exactly replaces the deficient secretion. However, $2\frac{1}{2}$ (0.16 gm.) to 5 grains (0.325 gm.) of the desiccated substance by mouth three times a day, or a hypodermic injection of 1 c.c. of Antuitrin (the soluble extract in ampoules) at intervals of one to three days, will be suitable for an average case.

Hypodermic is sometimes more effective than oral administration, presumably because it obviates the possibility of impairment from contact with the digestive secretions.

Posterior Lobe Therapy.

As Pituitrin so fully represents the activity of this portion of the pituitary gland, the disorders in which posterior lobe preparations are likely to be of service will be considered under the description of that well-known product, although the desiccated lobe in tablet form has been administered successfully in certain cases, particularly in the feminine type of obesity associated with increased carbohydrate tolerance, subnormal temperature, and drowsiness. In such cases the dose should be 1 to 2 tablets (equivalent to 3 to 6 grains of the fresh substance) an hour before meals, twice or thrice daily.

Pituitrin.

The aqueous extract of the posterior or infundibular portion of the pituitary gland was introduced into medicine by Parke, Davis & Co.,

in 1908. It is standardised physiologically by a determination of its constricting effect on the isolated uterus of the virgin guinea-pig (the oxytocic test), and by its effect on the blood pressure of anaesthetised dogs (the pressor test).

The use of Pituitrin in **obstetrics** is now definitely established, and when used judiciously in certain obstetrical conditions, it is one of our most reliable therapeutic agents.

Its main indication is in uterine inertia in which there would otherwise have been a normal delivery. When Pituitrin is used it is important that the following conditions should be present?—

- (1) Head engaged. (2) Cervix dilated. (3) No disproportion between the size of the passage and the passenger. (4) No mechanical obstruction to the delivery of the child. (5) Absence of high retraction ring.

From this it will be gathered that Pituitrin should not be given during the first stage of labour, in fact, the practice of giving Pituitrin as a routine measure before the second stage of labour is completed, or at any time merely to hasten the expulsion of the child, cannot be too strongly condemned. It is also inadvisable to administer it in complete inertia, or when scars are present in the uterus from a previous Cæsarean section, owing to the risk of uterine rupture.

Certain other conditions may be taken as contra-indications to the use of Pituitrin, viz., cardiac disease with high blood-pressure, eclampsia when the blood pressure is likewise high, and threatened asphyxia of the unborn child. Pituitrin should not be given when the foetal heart is irregular and its rate abnormal.

The indications for Pituitrin in obstetrical cases are excellently summed up by Cleveland in the *New Orleans Medical and Surgical Journal* for May, 1922.

He suggests its employment in (1) weak pains in the second stage of labour and occasionally near the end of the first stage if the cervix is dilatable. This is by far the most common indication. (2) In the second stage when the pains are weak and the patient is in "twilight sleep" or under an anæsthetic. (3) In accidental hæmorrhage—*abruptio placentæ*—when the head is engaged and the membranes have ruptured. (4) Having changed a face into an occipital presentation, strong pains are needed to force the occiput down on the perineum. (5) In the third stage, after the delivery of the placenta, to cause retraction and contraction of the atonic uterus. (6) In post-partum hæmorrhage from atony. (7) In the puerperal stage when there are clots or pieces of placenta in the uterus. (8) In late puerperal hæmorrhage. (9) In Cæsarean section, directly into the muscle if the uterus does not contract promptly. (10) To control bleeding following curettage after miscarriage. (11) Some good results have been reported in cases of urethritis and endometritis resulting from puerperal infection.

It is now generally agreed that the obstetric dose of Pituitrin should be small, three to four minims (0.2 c.c.) to begin with are generally sufficient and, if well tolerated, may be repeated or even increased, at intervals of thirty to forty minutes, to a point at which the desired expulsive contractions are produced. The use of 0.5 c.c. is to be preferred for a second dose, 1 c.c. doses being seldom necessary.

In cases of **post-partum hæmorrhage** an injection of Pituitrin (0.5 c.c. to 1 c.c.), particularly if made into the wall of the uterus during the operation of Cæsarean section, will cause a rapid contraction of the uterus, but in order to make the effect more persistent an injection of Ergot Aseptic may be given soon after the Pituitrin.

Pituitrin is administered by hypodermic injection, preferably into a muscle, in any convenient location that the physician may select.

Pituitrin has given good results in the treatment of **metrorrhagia**. Bab employed it in thirty cases. In ten, the hæmorrhage stopped one day after the injection; in eleven, two days thereafter; and in seven, between four and eight days thereafter. Bab believes we have in Pituitrin a potent remedy for metrorrhagia that has often proved of service when hydrastis, ergot and similar drugs were of no avail. He has observed surprising results not only in cases of **endometritis**, **metritis**, and **menorrhagia**, which were possibly due to increased ovarian action, but also in **hæmorrhages** due to myomata, ovarian cysts, or inflammatory diseases of the adnexa. He administered the Pituitrin in doses of two or three cubic centimetres, this amount being injected subcutaneously once or, according to indications, on several days in succession. The only after-effect observed, and that only occasionally, was uterine cramps resembling labour-pains.

The tonic action of Pituitrin upon the arterial system has led to its employment for combating **shock** and **collapse**. A single intravenous injection of 0.2 c.c. to 1 c.c., well diluted with warm physiological salt solution, influences arterial tone for upwards of an hour without producing abnormally high blood pressure. The hypodermic injection of 1 c.c. immediately after operation, and again at the third, sixth and ninth hours after, averts shock. Pituitrin injections are also valuable for counteracting low blood pressure in acute conditions such as pneumonia, acute bronchitis, diphtheria, cholera, typhoid fever, phthisis, etc., for the relief of tachycardia and the nervous symptoms of exophthalmic goitre. It has been suggested, also, in the treatment of certain forms of **epilepsy**.

Klotz strongly advocates the use of Pituitrin in **peritonitis** and in infectious diseases in which a reduction of the blood-pressure is produced by the existing toxæmia. At the same time he calls attention to the fact that it is contra-indicated in cases already exhibiting an increase of blood-pressure, *e.g.*, nephritis, the cardiac complications of goitre, etc., as well as in arterio-sclerosis and cardiac weakness.

A writer in the *Medical World*, September 29, 1922, states that in **hæmoptysis** the best immediate remedy is an intramuscular injection of 0.5 to 1 c.c. of Pituitrin. According to this author, Pituitrin is the only drug known which lowers pulmonary pressure whilst increasing systemic pressure; he uses it as a routine in all severe hæmoptyses and has had better results than with any other drug.

Houghton and Merrill have shown that the elevation of the blood-pressure produced by Pituitrin sometimes lasts half an hour or even longer. Klotz, more recently, observed an increase in the blood-pressure after the intramuscular injection of Pituitrin, which caused the mercury to rise from 15 to 30 mm. and lasted from fifty minutes to thirteen hours.

Beck and O'Malley also investigated the action of Pituitrin on the blood-pressure and incidentally on the pulse. They found that pituitary extract increased the blood-pressure and diminished the pulse-rate, the degree depending upon the dose of the extract and the susceptibility of the individual. The rise in blood-pressure varied from 8 to 38 millimetres, while the pulse-rate fell 4 to 17 beats per minute. No untoward effects were noted in any of the cases in which large or repeated doses were administered. They conclude their interesting paper by stating that the inhibitory influence upon the pulse is more lasting than the influence upon the blood-pressure.

Owing to its stimulant action upon unstriated muscle fibre, Pituitrin has been employed in the treatment of **post-operative intestinal stasis**. Its effect in intestinal stasis is to promote peristalsis, thus restoring normal bowel movement and preventing or relieving the painful accumulation of gas in the colon. It is of exceptional service in **ischuria paradoxa**, and its timely use will frequently render catheterization unnecessary after labour and surgical operations. For the latter purpose 1 c.c. of Pituitrin may be given and repeated at intervals of four to six hours if necessary.

The usual initial dose of Pituitrin in surgical cases is 0.5 to 1 c.c. (8 to 16 minims) administered immediately after operation and before the patient is put to bed. The dose may be repeated every three or four hours, if desired. This use of Pituitrin reduces the risk of shock.

The action of Pituitrin on the blood-vessels is very similar to that of Adrenalin, the active principle of the suprarenal gland. But the rise in blood-pressure following the administration of Adrenalin is quite transient, while with Pituitrin it persists, sometimes, for hours, and the heart action is slowed. The difference is explained by the fact that Pituitrin exercises a direct action on the muscular coats of the arteries.

Howell has observed that the increase in blood-pressure produced by successive injections of Pituitrin becomes less and less marked until no reaction at all occurs.

The fact that it exercises a more prolonged constricting influence upon the arterioles than that produced by Adrenalin has led to Pituitrin being used in the treatment of **hay fever** and **asthma**. In the *Medical Times*, May, 1917, Satterthwaite reported that pituitary extract, by reason of its relaxing effect on smooth muscle fibres, proved useful in the bronchial spasm of asthma. Some authorities oppose the use of Pituitrin in asthmatic patients on the ground that it is an antagonist of Adrenalin in its effect on the bronchi. It is now generally considered, however, that better results are obtained by a combination of Pituitrin and Adrenalin than from either agent alone. Krause expresses the opinion that the pituitary principle sensitizes the respiratory centre or the bronchial muscles to the action of the Adrenalin and thereby intensifies and prolongs the effect. (*Therapie der Gegenwart*, No. 7, 1913.)

The suggested dose of such a combination is an injection consisting of 2 to 6 minims of Adrenalin Solution and 8 minims of Pituitrin. During the intervals between attacks injections of Adrenalin and Pituitrin, repeated daily for a week and then on alternate days for another week, will, in many cases, lengthen the intervals between paroxysms and diminish their severity.

Zueblin records excellent results from the injection of a combination of Pituitrin and Adrenalin in hay fever cases. He repeats the dose in gradually diminishing amount when the increase in systolic pressure and pulse pressure, caused by the previous dose, is beginning to subside, cautioning the patient to avoid excessive exertion for a time after each dose. (*New York Medical Journal*, July 13, 1918.)

In the treatment of **enuresis** Pituitrin has been attended with most gratifying results. In the thyroid section, page 126, reference is made to the administration of desiccated pituitary gland in combination with desiccated thyroid in the treatment of this condition. In cases in which it is possible to administer hypodermic injections, Pituitrin will give much better and more rapid results. Since there is no gravid uterus to take into consideration, the dose of Pituitrin may be much larger than that given for obstetrical purposes; the dose suggested is 0.5 c.c. every day or every two days, by hypodermic injection. In children or where for any reason hypodermic injection is deemed inadvisable, the dose may be placed under the tongue. In the majority of cases 0.5 c.c. is well borne, and a few injections will usually result in marked amelioration of the bladder condition. The intervals between bed-wetting will be gradually lengthened until the child has perfect control over bladder function. Occasionally this dose may produce intestinal cramps, in which case it should be reduced.

In view of the accepted pathology of **diabetes insipidus** as a defect in the pituitary body, particularly the posterior lobe, the administration of Pituitrin as a palliative measure seems entirely rational. Generally the injection of 1 c.c. will cause polyuria to disappear in about twelve hours.

In the section on Diabetes Insipidus in the volumes entitled "Endocrinology and Metabolism," edited by Barker, Hoskins and Mosenthal, Williams states that in his opinion the most useful agent thus far discovered is the extract prepared from the posterior lobe of the hypophysis, familiarly known as Pituitrin. To be effective, the extract must be given hypodermically. The dose usually recommended in this condition by most writers is 1 c.c. daily. Intravenous injection is inadvisable and not without danger. Within a few minutes after subcutaneous administration, the author says, the patient may complain of ringing in the ears, dizziness, or headache, but these symptoms soon pass off, as does also the intense craving for water. For the following eighteen to twenty-four hours the patient will have a feeling of well-being and comfort due to the cessation of the extreme thirst and excessive urination. Toward the end of the twenty-four hour period the symptoms begin to return, and the treatment must be repeated if relief is to be maintained.

Pituitrin relieves the symptoms of diabetes insipidus while it is being administered, but treatment looking towards a cure must, of course, provide for removal of the cause of the pituitary hypofunction if possible. Syphilis, especially, must be looked for, as some cases of diabetes insipidus are the result of gummata in the pituitary body.

ADMINISTRATION OF PITUITRIN.

Pituitrin may be given orally, but with less effect than when given hypodermically; nevertheless this method appears to have been satisfactory in certain cases in which there were objections to the use of the subcutaneous method.

It has also been claimed that Pituitrin may be sprayed into the nose for its systemic effect. Allen and Sherrill (*Journal of Metabolic Research*, 1923, Vol. 3, 479-510) report beneficial results in diabetes insipidus by spraying 0.2 to 0.3 c.c. into the nasal chambers. Pituitrin, given either subcutaneously or by nasal spray, they state, shows its usual effect in reducing the thirst and the polyuria.

In obstetrical cases and in cases of hæmorrhage the necessity for prompt effect will usually preclude the oral use of Pituitrin; but in other conditions it may be given by mouth or placed beneath the tongue of the patient and retained there to be absorbed by the sublingual tissues. Particularly in the bed-wetting of young children, Pituitrin by mouth has been preferred by many owing to the patient's fear of the needle. To meet this need, tablets containing 3 grains (0.2 gm.) of fresh posterior lobe substance are supplied for oral administration. (See List of Pituitary Gland Products.)

Pituitrin administered either *per os* or subcutaneously, is well borne. Published reports show that it may be given in relatively large doses, except in confinement cases. Deep intramuscular injections are preferred to subcutaneous by some experienced operators.

The Whole Gland.

Disorders of the whole gland display various combinations of symptoms caused by defects in the secretions of its component lobes. Thus there may be (1) hypoactivity of both lobes ; (2) hyperactivity of both lobes ; and (3) heteroactivity. The last named comprises mixed cases in which the lobes have opposite disorders of function—for example, an excess of anterior lobe secretion with a deficiency of posterior lobe secretion, or *vice versa*.

Diagnosis must be based on the presence or absence of symptoms generally recognized as caused by an excess or deficiency of the anterior or posterior lobe secretion. Under whole gland hypoactivity is classed adipose genital dystrophy (Fröhlich's syndrome), which is characterized by shortness of stature, genital aplasia, and posterior pituitary adiposity (lower abdomen and upper two-third of thigh). Under whole gland hyperactivity are grouped cases of gigantism or acromegaly and glycosuria, with which increased metabolism and decreased sugar tolerance, without adiposity, are associated.

According to Engelbach (*Endocrinology*, July-September, 1920, Vol. IV, No. 3, 347-365), the heteroactive varieties of bilobar pituitarism should contain cases manifesting a hyperactivity of one lobe and a hypoactivity of the other. Gigantism or acromegaly, when associated with polyuria, would naturally be placed in the heteroactive bilobar variety. A considerable percentage of these cases, he states, show evidence of anterior lobe hyposecretion (such as genital aplasia and infantilism, amenorrhœa, sexual impotence, muscle fatigue, and mental apathy), associated with posterior lobe hyperactivity (such as pituitary glycosuria, with increased metabolism and decreased sugar tolerance).

It must be borne in mind that the symptoms manifested in cases of anterior lobe deficiency or excess vary in character according to the time of occurrence of the deficiency or excess in relation to puberty and epiphyseal fixation in the long bones. The same variation is to be noted in bilobar diseases, on account of the fact that symptoms and signs referable to the anterior lobe play a considerable part in the syndrome.

Thus in certain cases the posterior lobe obesity occurs in a patient of normal height and with the genital organs fully developed, but with other evidence of anterior lobe defect. This is accounted for by the fact that the anterior lobe deficiency did not take place until after puberty and epiphyseal ossification.

In such cases there may be more or less complete disappearance of the menses in the female, with other symptoms of genital disorder, such as frigidity, sterility, etc., but the secondary sex characteristics are present. Loss of libido, and impotence, may be manifest in the male. Somnolence, amounting almost to hibernation, may be a distressing symptom.

Other symptoms frequently accompany those of greater diagnostic significance. There may occur severe attacks of headache, vertigo, hot flushes, cold sweats, nausea, vomiting, gaseous abdominal distention, constipation, visual scotomata, slow pulse, mucous colitis, syncope, epileptiform attacks, pains in different regions, etc. Constitutional symptoms are more likely to occur in cases in which the anterior lobe insufficiency was post-adolescent or developed quite late in life. Their severity appears to increase with the age of the patient at the time of their first appearance.

In the male, lack of development of the genital system, resulting from anterior lobe insufficiency, is accompanied by feminine conformation of the body and a more or less feminine mentality. Axillary and pubic hair is absent or is of the lanugo type, and the mammary folds are large. In the female the usual symptoms of sex subnormality are present: the vulva is of the infantile type, and the breasts are small or almost entirely devoid of development. In both sexes the fingers are tapering, the head is small and round, and the small bones of the extremities are extremely delicate. In bilobar disorders the usual symptoms of posterior lobe deficiency or hyperactivity, cited heretofore, are engrafted on the foregoing.

Cases in which there is a hyperactivity of a part or the whole of the gland are obviously not suitable for substitution therapy. It is well to remember, however, that certain patients who at one time were subject to oversecretion may later manifest symptoms of deficiency that may well be counteracted by the administration of a suitable gland product.

Perhaps the outstanding indication for the administration of the desiccated substance of the whole gland is **adipose genital dystrophy**. As this condition is due to insufficiency of the anterior lobe as well as of the posterior, the rational substitution treatment is to supply a preparation containing both lobes. The dose should be about 6 grains (0.4 gm.) daily of the fresh gland.

The oral administration of pituitary gland substance is also likely to be beneficial in cases of **uterine atony** and in various chronic non-inflammatory gynaecological affections, the results apparently depending on improvement in vascular and muscle tone and, perhaps, a change in ovarian function. Doses of 4 to 6 grains (0.25 to 0.4 gm.) *per diem* often prove beneficial in young women of faulty development with uterine atony and a troublesome discharge due, apparently, to muscular relaxation. In some cases it is of advantage to give ovarian substance with the pituitary, and a small dose of thyroid substance at night.

The administration of pituitary gland is said to relieve that peculiar type of intractable **frontal headache** which has been attributed to disease or exhaustion of the pituitary gland.

In replacing insufficient secretion of both lobes, a preparation made from the whole gland may be prescribed, or a combination of anterior and posterior lobe preparations may be employed instead. Anterior Lobe in tablet form, $2\frac{1}{2}$ or 5 grains, three times a day, may be orally administered coincidentally with the hypodermic injection of Pituitrin at intervals of one to three days. Or Antuitrin may be employed hypodermically instead of anterior lobe orally. When so desired, one Posterior Lobe Tablet, 3 grains, after each meal, may replace the Pituitrin.

It should be borne in mind that it is not uncommon for pituitary insufficiency to be accompanied by hypothyroidism. Careful study of certain cases has led to the conclusion that a deficiency of the thyroid and a lack of pituitary secretion frequently occur together, or the former follows the latter. In such cases the lessened thyroid secretion should be compensated by the administration of fresh thyroid gland in doses of $\frac{1}{2}$ to 5 grains or more three times a day, the dosage to be adapted to the needs of the individual patient. This must of course be accompanied or succeeded by a course of the proper pituitary preparation. Such treatment will have to be continued for an indefinite period.

THE OVARIES.

The ovaries in mammalia consist of a connective tissue stroma with blood vessels, lymphatics and nerves, enclosing the Graafian follicles with the ova. Cyclical changes occur in both the ovary and the uterus. In the ovary these consist of ripening of the follicle, ovulation, and formation of the corpus luteum. In the uterus, on the other hand, structural changes accompany the œstrous cycle, consisting of growth of the mucous membrane with increased glandular activity, followed by regression and period of rest. It is obvious that both the ovary and the corpus luteum are intimately associated with menstruation; in all probability, the ovary controls ovulation whereas the corpus luteum inhibits it. On the other hand, menstruation would appear to be stimulated by both the ovary and the corpus luteum. The true explanation will probably be found in a delicate adjustment between these two, the ovary governing the periodicity and the corpus luteum causing the decidual changes and the rhexis.

The function of the corpus luteum in preparing the uterus for pregnancy is generally recognised, and it seems highly probable that its action in menstruation is exerted upon the endometrium. After ovulation the corpus luteum lasts for about two weeks, then disappears; this is the corpus luteum of menstruation.

If conception has taken place the corpus luteum persists and becomes the true corpus luteum of pregnancy, increasing in size until about the third month of pregnancy, when it gradually shrinks and finally disappears. During these early months it supplies a secretion that is

essential to the maintenance of the endocrine balance. If that secretion is deficient the woman develops hyperemesis of pregnancy.

In addition to controlling ovulation and partially controlling menstruation, the ovary is known to have an important bearing on the development of the secondary sex characters. As the result of extirpation of both ovaries the individual loses the feminine voice, grows hair on the upper lip and chin, and acquires a straighter and more masculine contour.

In the human subject, extirpation apparently leads to a series of symptoms which are usually attributed to excitation of the autonomic nervous system; these consist of emotional disturbances, headache, fainting, intestinal disturbances and feelings of heat and cold.

It has been observed that girls' legs stop growing when they begin to menstruate. Thus, a girl whose menstruation has been delayed has long legs, and those in whom puberty sets in early have short legs. Cases in which there is ovarian insufficiency associated with increased growth of the lower extremities are called eunuchoids. (An analogous condition is found in men.) Such cases of gonadal insufficiency usually have a peculiar deposit of adipose tissue over the great trochanters. When it is present it is most striking, and should always be interpreted as an evidence of insufficient ovarian activity or, in the man, of insufficient testicular activity.

The ovaries appear to antagonise the parathyroids. Thus, hyperactive ovaries cause rapid calcium depletion, which may go on to the extent of producing osteomalacia.

With respect to the endocrine system generally, the ovaries have a definite relationship to two groups of glands. One group, consisting of the thyroid, pituitary and suprarenals, supports them in their function, while the other group, consisting of the thymus, placenta, corpus luteum, and the mammary gland, represses them in their action.

Certain physiological phenomena point to the correctness of this view. The disappearance of the thymus is coincident with the functional development of the ovary. Persistent thymus means underdevelopment of the ovary and the other generative organs, also of the sex characteristics.

The placenta makes its appearance when the ovary, and especially its menstrual function, must be held in abeyance. Probably the action of the placenta is directed against the posterior pituitary, whose secretion (pituitrin) would set up uterine contractions and terminate pregnancy. At term, the balance between the placenta and the pituitary is disturbed in favour of the latter, with the resultant induction of labour.

The corpus luteum, although morphologically a part of the ovary, seems at times to repress ovarian function. It is in the ascendancy, and its secretion is much increased, when the ovary must be repressed

in its activity. The corpus luteum and the placenta seem to move in the same orbit in their action of eclipsing the ovary and the pituitary. The corpus luteum acts in early pregnancy; the placenta takes up the duty when gestation is more advanced.

The mammary gland begins its eclipse of the ovarian function during the puerperium when the placenta or the corpus luteum can no longer serve in this capacity. Menstruation and probably ovulation usually do not make their reappearance until the lactating function of the mammary gland tends to decline. Incidentally, the mammary gland has a potent influence in contracting the uterus (involution) after the expulsion of the products of conception.

So much for the glands that control the ovary. What influence have the three that support it?

Briefly, the thyroid assists the ovary in the discharge of its trophic and developmental duty; the pituitary assists the ovary in exerting its influence on uterine contractions; the suprarenals together with the thyroid help in the performance of the catamenial function. It has been proved that the injection of an extract of ovarian substance immediately increases the flow of pituitrin into the cerebro-spinal canal (*Journal of Physiology*, March, 1923). The author shows that ovarian extract is the only animal extract so far examined, apart from posterior pituitary, which produces an immediate secretion of the pituitary gland. The earlier experiments were made from fresh tissue, but in a further series of experiments the extracts prepared by Parke, Davis & Co. were used: (1) the whole ovary, (2) the ovary from which the corpus luteum had been removed, and (3) the corpus luteum. The corpus luteum was without any action on the pituitary secretion, but the other two extracts immediately excited the pituitary to secrete; the secretion of pituitrin commenced about twenty seconds after their injection and was present in excess for a minute or two, when the cerebro-spinal fluid became normal. It seems clear that ovarian conditions determine the secretion of the pituitary, and thus react indirectly on the uterine tonus.

Ovarian Therapy.—In employing ovarian products in therapeutics three kinds of preparations are available, and each has certain special indications. There is a preparation made from the whole gland, which is called Ovarian Substance, and is supplied in tablets, also in soluble extract for hypodermic injection; another is pure Corpus Luteum, which is supplied in powder, capsules, tablets, and in soluble extract for hypodermic injection; and a third, made from the ovary after ablation of the corpus luteum, is called Ovarian Residue, and is available in powder, in tablets, and in soluble extract for hypodermic injection.

Ovarian Substance (whole ovary).

For use in medicine, the entire ovaries from pregnant cattle are freed from fat, dried at a low temperature, and powdered. The

powder is made up into chocolate-coated tablets containing either 1 grain (0.065 gm.) or 5 grains (0.325 gm.) of the desiccated substance. A fluid containing the soluble principles of the gland is also prepared from the powder, and is supplied in ampoules containing 1 c.c.

The administration of ovarian substance is indicated, in general, in **hypo-ovarism**, especially in delayed development of the generative organs or of feminine characteristics (breast, hips, voice, etc.), and in the physical and mental disturbances of the **menopause** or subsequent to oöphorectomy.

Ovarian insufficiency is sometimes an underlying cause of **obesity** in women; it may also play a part in the etiology of rheumatic pains, exophthalmic goitre, various psychoses and pluriglandular syndromes. **Simple goitres** in which the thyroid is attempting to compensate for ovarian hyposecretion, as often seen in young girls, rapidly disappear under ovarian treatment. In **chlorosis** this substance often proves a valuable auxiliary to iron treatment.

In the treatment of **eunuchoidism**, the administration of ovarian substance should be pushed to the limit; and while, of course, the peculiar skeletal anomaly will not be corrected, the physician will frequently be rewarded by seeing the unmistakable development of the secondary sex characters and normal sexual function.

There would appear to be grounds for believing that ovarian therapy may have some value in the treatment of **sterility**. A number of cases are reported in which women, after having had no periods, have begun to function regularly after the exhibition of ovarian substance and a short time later have become pregnant.

Hirst, writing in the *New York Medical Journal*, October 5, 1921 states that ovarian extract, intravenously, is now his routine practice in all cases of hysterectomy. His method is to begin the injections on the third day after operation and continue them until the patient leaves the hospital on the twenty-first day. In cases associated with the **menopause** he gives the whole ovarian extract orally, but states that results are not invariable with any extract, they are often slow, particularly in menstrual disorder, and patience is frequently necessary.

Thyroid preparations constitute a valuable addition to prescriptions for ovarian products, because of the close physiological relationship existing between the two glands. For this purpose, Thyrovarian Compound Tablets are useful (see page 161).

DOSAGE.

The average dose of desiccated ovarian substance is 5 grains (0.325 gm.) daily, although in some instances it may be desirable to increase this to 10 grains (0.65 gm.). The dose is preferably given between meals. Of the soluble extract 1 c.c. may be injected intramuscularly every day or on alternate days.

As administration is for the purpose of compensating for an organic deficiency, treatment may need to be maintained for a long period, or may have to be renewed from time to time if symptoms recur after an apparent cure.

Ovarian in Combination with other Glands.—In view of the important relationship which exists between the ovaries and the other ductless glands, there is evidence that a combination tablet is often useful in certain conditions. The fact that the suprarenal and pituitary glands are important synergists of the ovaries is an indication that a combination of these three glands is sometimes more effective than ovarian substance alone in remedying the various manifestations of ovarian insufficiency. Such a combination is available under the name of **Ovarian Compound Tablets**, each tablet containing 2 grains (0.13 gm.) of desiccated ovarian substance, and 1 grain (0.065 gm.) each of desiccated suprarenal and pituitary whole gland. Such a combination as this will often relieve the strain of puberty and the difficulties of glandular readjustment in cases of surgical or natural menopause.

It sometimes happens that ovarian substance is better combined with suprarenal and thyroid, and this combination can be supplied under the name of **Thyrovarian Compound Tablets**, each tablet containing 3 grains (0.2 gm.) of desiccated ovarian substance, 1 grain (0.065 gm.) of desiccated suprarenal and $\frac{1}{2}$ grain (0.03 gm.) of desiccated thyroid gland.

The dose of either of these compounds is one tablet, two or three times daily between meals.

Ovarian Residue.

In the preparation of Ovarian Residue, the ovaries from cattle, after the careful removal of the corpus luteum, are desiccated, freed from fat, and powdered. The product is available in tablets containing 5 grains (0.325 gm.) of desiccated material, also in soluble extract for hypodermic administration.

The question as to whether the interstitial portion of the ovary (ovarian residue) should be classed with other glandular extracts from the standpoint of hormone activity has hitherto been a debatable one, but, in the light of recent histological and physiological research, backed up by clinical evidence, there would appear to be ample proof that this portion of the ovary does elaborate an internal secretion quite separate and distinct from that of the corpus luteum. The influence on the growth of the child, as shown by early ovariectomy, is evidence in this direction, seeing that it is exerted at a time when normally no corpora lutea would be present. Equally striking is the homology existing between the interstitial cells of the ovary and the interstitial cells of Leydig, cells which are known to be secretory in nature. It has already been pointed out that the trend of opinion in the matter of

ovarian physiology is towards the belief that the corpus luteum collaborates with the interstitial secretory cells of the ovary in producing menstruation, the latter regulating the periodicity and the former causing the hyperæmia of the endometrium and the rhexis. Furthermore, there is ample justification for the belief that the interstitial secretion controls the secondary sex characters and ovulation. It is on these grounds that Ovarian Residue has been tried in the nervous symptoms of the **menopause**, both natural and artificial, in **disturbances of menstruation**, and in cases of **sterility** attributable to disturbed or faulty ovulation. Graves (*Surg., Gyn. and Obst.*, December, 1919) states that in post-operative hot flushes Ovarian Residue acts as a specific palliative, rarely failing to give some degree of relief. Such symptoms as dizziness, sleeplessness, headaches, muscular pains, buzzing in the ears, asthenia, etc., which are so common in the natural menopause, are often helped by Ovarian Residue.

Referring to **amenorrhœa**, Graves states that in some cases where the menstruation was merely delayed, the results were striking, but even in long-standing cases in which the menstrual rhythm could not be re-established, patients often spoke highly of the tonic effect of the treatment. Tyler (*Ther. Gazette*, January, 1920) details his experience with Ovarian Residue, principally in cases of **menorrhagia** and **metrorrhagia** with clotting. According to this author it is perfectly rational to employ Ovarian Residue in amenorrhœa and menorrhagia—two apparently opposite conditions—because the regulating influence that is lacking is rhythmic, controlling the periodicity of the flow rather than the quantity. Tyler came to the conclusion that in his series of cases, with and without palpable pelvic pathology, the remarkable action of Ovarian Residue was shown in the absolute certainty with which the amount of the menstrual flow could be reduced, in the disappearance of the clots, and especially in the lengthening of the intervals between the period in cases of metrorrhagia.

On the whole, it may be laid down that the administration of Ovarian Residue is indicated, in general, in those cases in which it is desired to cause ovarian stimulation without increased activity of the corpus luteum. It follows, therefore, that Ovarian Residue should be prescribed in all cases of amenorrhœa, oligomenorrhœa, and dysmenorrhœa which are associated with any degree of asthenia. The administration of Corpus Luteum or Ovarian Substance (which includes Corpus Luteum) in such cases would be likely to aggravate the asthenia.

DOSAGE.

The dose of Ovarian Residue, Desiccated, is from 5 to 20 grains (0.325 gm. to 1.3 gm.). Of the soluble extract, 1 c.c. may be injected every day or on alternate days.

Corpora Lutea.

For use in medicine the yellow bodies contained in the ovaries of *pregnant* cattle are carefully separated from the ovarian tissue, dried and powdered. Corpora Lutea, Desiccated, is supplied in bottles containing one ounce (28 gm.), in capsules containing 5 grains (0.325 gm.) and in tablets containing 2 grains (0.13 gm.); a soluble extract is also prepared for hypodermic injection.

The administration of Corpora Lutea is indicated in **delayed or scanty menstruation** of sthenic type, in **dysmenorrhœa** with a tendency to clotting of the blood, in the **pernicious vomiting of pregnancy**, and in selected cases of **sterility** and **habitual abortion**. Some endocrinologists assert that it may be employed as a symptomatic remedy in hyperthyroidism and in functional high blood pressure because it is capable of quieting the tachycardia in the one case and lowering the systolic pressure in the other. It has likewise been recommended by clinicians in the treatment of the disturbances attending the natural or artificial **menopause**, although for this purpose Corpora Lutea is generally not so effective as the entire Ovarian Substance. The same applies in the psychoneuroses of the menopause. In cases of **pruritus vulvæ** or **kraurosis vulvæ** the value of Corpora Lutea is less certain, although some observers have apparently had excellent results. Probably the chief indication for the administration of Corpora Lutea is the **hyperemesis of pregnancy**. Hirst (*New York Medical Journal*, October 5, 1921) reports favourable results in 89% of his cases. The majority of his patients were relieved by a series of twelve doses of the soluble extract, 1 c.c. being given daily by intramuscular injection in the mild cases, and 2 c.c. intravenously twice daily in the severe cases. This observer states that goitre is a contra-indication. Hirst also reports success with Corpora Lutea in cases of **habitual abortion**. It is important, however, that, as far as possible, those cases only should be treated which could reasonably be regarded as due to deficiency or absence of corpus luteum secretion. Treatment of patients having a history of repeated miscarriages was begun as soon as the patient found she was pregnant, and consisted of twenty-four daily injections of 1 c.c. of Corpora Lutea Soluble Extract. Three of the four patients reported upon went to full term.

Metrorrhagia and **menorrhagia**, provided they are manifestations of hyperactivity of the ovary, are also indications for the use of Corpora Lutea. If thyroid is combined with the corpus luteum great care must be exercised to make the period over which the combination is administered a short one, because both drugs are potent and one of them, namely, Corpora Lutea, is decidedly depressant at times, a fact that has to be taken into special consideration in employing corpus luteum preparations therapeutically.

A writer in *The Medical Press*, April 12, 1922, refers to the administration of Corpora Lutea in certain cases of **sterility**. For a patient who

has scanty menstruation, or none, the result following a course of Corpora Lutea is in some cases very gratifying. The dose recommended by this writer is 5 grains (0.325 gm.) daily for two days, this amount to be gradually increased until at the end of a month 10 grains (0.65 gm.) are being taken three times daily.

The Journal of Obstetrics and Gynæcology, No. 4, 1924, p. 580, contains a report by an eminent gynæcologist, who claims that he has had 75 per cent. of successes in cases of sterility treated with corpora lutea.

DOSAGE.

2 to 5 grains (0.13 to 0.325 gm.) of the powder or tablets to be taken at least one hour before meals three times daily. One 5 grain (0.325 gm.) capsule may be given once or twice a day. Intravenous or intramuscular injection appears to give even better results than oral administration, and 1 c.c. of the soluble extract may be injected daily or on alternate days in severe, and twice a week in less severe cases.

THE MAMMARY GLAND.

Endocrinologically the function of the mammary gland appears to be to antagonise the ovary in both its ovulating and menstruating activities. If we consider the chronological development of the true corpus luteum, the placenta, and finally the mammary, we find that the woman is provided with a series of ovarian antagonists at the very time when it is undesirable to have ovarian activity, that time being the period of gestation and the period of lactation.

With the beginning of the puerperium, when the true corpus luteum has long been in abeyance and the placenta is no longer present, the mammary gland steps into the breach as a check on the ovaries. A lactating woman rarely menstruates, and hardly ever ovulates. The laity are familiar in a vague way with the contraceptive power of the mammary hormone, and many women prolong unduly the period of lactation because of the dread of another pregnancy. Such prolonged lactation, and occasionally excessive mammary activity of shorter duration, causes hyper-involution of the uterus, commonly known as lactation atrophy. This may be an amplification of the phenomenon noticed at the child-bed when the baby is put to the mother's breast to cause uterine contractions.

The administration of mammary substance has been found helpful in cases of **subinvolution** of the uterus, particularly in the absence of malignancy or structural change.

One writer states that mammary substance has proved valuable in **metrorrhagia of the climacteric**, and for controlling hæmorrhage due to uterine sclerosis and fibroids, as well as the indefinite uterine oozing of the menopause not associated with malignant growths;

also that its property of depleting the uterine blood-vessels renders it useful in **ovarian congestion** due to salpingo-oöphoritis or other cause.

Other reports state that in cases of **uterine fibroids** the administration of mammary substance has caused the tumour to disappear, or to diminish perceptibly, and has reduced pain and bleeding. In cases of **neurasthenia, hysteria, epilepsy**, etc., associated with gynæcological affections, mammary substance has been found to exert a sedative influence.

Mammary Gland Therapy.

For use in medicine, the mammary glands of lactating cattle are carefully desiccated, powdered, and made into tablets (chocolate-coated) each containing 5 grains (0.325 gm.) of the desiccated substance. As a therapeutic agent, desiccated mammary gland is the most effective antagonist of the ovary at our disposal. All types of **dysmenorrhœa** caused by ovarian hyperactivity are usually relieved by the exhibition of this preparation in doses of 2 or 3 grains (0.13 or 0.2 gm.) three times a day. Cases of **menorrhagia** in which the flow is unduly prolonged can generally be corrected by beginning the administration of mammary substance on the third day of the menstruation. In cases in which the menstrual flow comes on too soon, it can be deferred and made quite normal by giving mammary substance for a week before the expected menstruation.

Reference is made on page 166 to the combined use of placenta and mammary substance in cases of excessive and irregular uterine bleeding. This combination has also been suggested as a galactagogue.

DOSAGE.

The dosage of desiccated mammary substance is 5 to 10 grains (0.325 to 0.65 gm.), before meals, twice or thrice daily.

THE PLACENTA.

The placenta occupies a unique position as an endocrine gland because it is present only during pregnancy. It begins to develop immediately after conception, and continues to secrete its hormone until it is separated from the uterine wall during labour. Its function has not been definitely determined, but the most likely explanation of its action is that it antagonises ovarian and posterior pituitary activity, and that it augments hyperplastic development of the mammary glands. Whether or not it actually promotes the secretion of milk is doubtful.

Some observers go so far as to say that the placenta inhibits the secretion of milk, although they admit that it prepares the breast for such secretion by stimulating the hyperplastic changes—they point to the fact that frequently the mother does not secrete milk until the placenta has been expelled. On the other hand, those who adhere to the view that the placenta actually promotes milk secretion are

supported to some extent by the fact that in the case of some animals which are the most prolific producers of milk the placenta is devoured by the mother. This controversy concerns only the quantity of milk secretion. When it comes to the quality of the milk, there is no longer any doubt of the action of placental extract. It has been definitely shown that breast-fed children who do not thrive, frequently begin to pick up immediately upon administering desiccated placenta to the mother. The dose for such purposes should be as large as 15 to 20 grains (1 gm. to 1.3 gm.) a day.

It is stated that the painful congestion and turgescence of the breasts that often accompany the establishment of lactation may be avoided if placental substance is administered before, during or just after parturition; also that the secretion of an adequate quantity of milk is favoured by the administration of 5 grains (0.325 gm.) of desiccated placental substance, thrice daily for one or two weeks before term. If not so administered, it is suggested that twice that quantity should be given at hourly intervals for six doses every third or fourth day while necessary.

A German physiologist is of opinion that the fully-developed placenta contains a substance possessing powerful oxytocic action displayed at the moment of parturition, and suggests that its administration might prove useful in cases of protracted labour; it has the advantage of being non-toxic.

Placental Therapy.

For use in medicine the fresh placenta from cows are thoroughly cleansed, cut up, carefully desiccated and reduced to powder, from which chocolate-coated tablets containing 5 grains (0.325 gm.) of the desiccated substance are prepared.

Based on the assumption that the placenta antagonises the posterior pituitary, the desiccated substance has been tried in cases of **dysmenorrhœa** characterised by a peculiar gnawing sensation such as might result from a temporary excess of posterior pituitary activity, and the clinical evidence is such as to warrant further use of the product in this condition. The best way to administer it is in daily doses of 10 grains (0.65 gm.) for two weeks before the expected menstruation.

In cases of **menorrhagia** and **metrorrhagia**, desiccated placenta has been given to check the flow and to shorten its duration if it is too long. The action of the product is notably enhanced if it is administered in combination with mammary substance. In such cases it is best to begin treatment about one week before the expected flow and continue it until menstruation is over. About 10 grains (0.65 gm.) of each product should be given daily in suitable doses.

Some endocrinologists have suggested administering desiccated placenta in cases of **threatened abortion** when caused by over-activity of the posterior pituitary; its inhibiting action on the ovary and

thyroid helps to delay the onset of menstruation and to check excessive bleeding.

Desiccated placenta is also said to be useful in **post-partum psychoses**, such as melancholia, and in severe **occipital headaches** or **migraine** in women, which also, in many instances, are due to over-activity of the posterior pituitary.

DOSAGE.

The average dose of desiccated placenta substance is 5 grains (0.325 gm.) three times daily.

THE TESTES.

In considering the testes as endocrine organs, the external secretion, the seminal fluid, must not be confused with the real internal secretion. The active part of the external secretion, the spermatozoön, is elaborated by the spermatogenic cells, whereas the testicular hormone is a product of the interstitial cells of Leydig, which is proved by the fact that the ligation of the vas deferens leads to atrophy of the seminiferous tubules, whereas the interstitial cells are not affected, and the secondary sexual characters develop normally. The external secretion is not essential to health, although it has considerable bearing upon virility. The function of the internal secretion is to control the development of the masculine sex characters and to promote sexual desire and sexual activity. The castrated male soon acquires feminine characteristics—enlargement of the breasts, adiposity, especially the trochanter pad, high voice, and the feminine distribution of hair, especially at the mons. If the castrate is young, he develops, in addition to the feminine attributes, the true eunuchoid appearance characterised by the extraordinarily long growth of the legs. During adult life a decline of testicular hormone activity is characterised by loss of libido, the sudden appearance of mammary and trochanteric fat, and occasionally the premature greying of the hair.

Orchic Substance Therapy.

For use in medicine, chocolate-coated tablets each containing 5 grains (0.325 gm.) of desiccated orchic substance (also known as testicular substance) are prepared as well as an Orchic Compound Tablet, the latter containing 3 grains (0.2 gm.) of desiccated orchic substance and 1 grain (0.065 gm.) each of desiccated suprarenal gland and desiccated anterior lobe pituitary gland. Another combination, under the name of Thyorchic Compound Tablet, is sometimes to be preferred; the formula is the same as that of Orchic Compound Tablets, with the exception that the anterior pituitary is replaced by $\frac{1}{2}$ grain (0.03 gm.) of desiccated thyroid.

Whilst, theoretically, it would appear that certain conditions afford clear indications for the administration of Orchic Substance, the

results obtained in actual practice have not been altogether consistent. It has been prescribed in cases of **neurasthenia**, **prostatic hypertrophy**, **impotence**, **hysteria**, and **hystero-epilepsy**, in certain forms of **obesity**, and as an **aphrodisiac**. In **premature senility** and premature loss of sexual vigour, Orchic Substance, reinforced by small doses of thyroid and anterior pituitary, has proved useful.

Orchic Substance has also been prescribed in certain forms of **nervous debility**, particularly the neurasthenic type. It is said to be useful in **mental conditions**, especially in dementia præcox and melancholia. It has been recommended in certain toxic dermatoses and even in psoriasis, the theory behind such treatment being that the gland may have an antitoxic action.

DOSAGE.

One tablet of plain Orchic Substance, or of either of the compound tablets, may be taken, usually before meals, once, twice or thrice daily, the dose being gradually increased if and as necessary.

THE THYMUS.

The thymus is an important gland in childhood. Its functions are to aid in the physical and mental development of the child and to prevent sex development—as Langdon Brown says, it acts like a brake on the development of sexual maturity. The thymus normally retrogresses with the onset of puberty; indeed, this retrogression makes puberty possible. Persistent thymus causes delayed puberty, and early decline of thymic activity results in sexual precocity.

Some authorities believe that the thymus plays an important part in the calcium metabolism of the body, and its removal in animals is said to result in calcium deprivation, giving rise to spontaneous fractures, osteomalacia, and other abnormalities. According to Sajous, the function of the thymus is to supply an excess of phosphorus in organic combination during the growth of the body—particularly while the development of the osseous and nervous system demands such a reserve—that is, before puberty or later if need be.

Thymus Therapy.

For use in medicine, the healthy thymus glands of the sheep are carefully desiccated and reduced to powder, from which chocolate-coated tablets containing 2 grains (0.13 gm.) of the desiccated substance are prepared. The indications for the administration of thymus gland substance may be stated in general to be those conditions in childhood which are associated with defective nutrition. **Mongolian idiocy** is said to be benefited by the use of a preparation of the thymus gland. Some clinicians have reported that desiccated thymus, in doses of about 6 grains (0.4 gm.) *per diem*, has given good results as an antagonist to the ovaries in cases of

menorrhagia and **metrorrhagia**. It is best given in combination with twice that quantity of mammary substance, which has a definite sedative influence on the ovaries. In **osteo-arthritis** good results have been reported from the free administration of desiccated thymus.

Some endocrinologists claim that thymus is useful in cases of rickets. It has also been used in **arthritis deformans** and delayed union of fractures. Owing to the fact that thymus is believed to have a balancing action on certain other endocrine glands, it has been used in order to counteract excessive secretion on the part of those glands; it has been tried in **exophthalmic goitre** and **colloid goitre**, but the results of the treatment are conflicting. Its use has also been suggested in cases of **simple goitre**. In hyperacidity of the gastric secretion associated with hyperthyroidism, thymus is said to diminish the mobilisation of chlorides and thus restore the secretion to its normal condition.

On account of its richness in proteins, thymus is contra-indicated in gouty patients and also during pregnancy.

DOSAGE.

The average dose of the desiccated material is 2 grains (0.13 gm.) three to five times a day.

THE PINEAL.

The precise function of the pineal gland is not clearly understood, although it is believed to be concerned with somatic and sexual development. The administration of pineal gland substance is, to a great extent, empirical, and clinical evidence so far available is mainly suggestive. The gland substance, however, is supplied with full assurance as to genuineness for physicians who may desire to use it, though no claim is made with regard to any remedial virtues that it may possess.

The administration of pineal gland substance has been adopted in the treatment of functionally **retarded mentality** in children without evident physical cause, such as defects of cranial bones or brain substance, adenoids, diseased tonsils, pituitary or thyroid disorder, and the results reported appear to warrant further trial in such cases. In cases of **premature mental failure** in later life, without distinct organic cause, the administration of pineal gland has been thought to exert a stimulating influence upon the sluggish brain.

DOSAGE.

The dosage suggested is one tablet, which represents 1/10 grain (0.0065 gm.) of the dried gland, thrice daily for several months. The dose may be increased or decreased as the effect may indicate.

GLAND PRODUCTS.

The Ratio of Fresh Gland to Desiccated Substance.

It is of the utmost importance that the dispenser should know whether fresh gland or desiccated substance is intended by the prescriber. A tablet labelled on its content of fresh gland is obviously much weaker than one containing a similar grainage of desiccated material. Inasmuch as one part of desiccated gland may be equivalent to 5, 6, 7, 8, or 10 parts of the fresh gland it is desirable that prescriptions should specify "sicc." or "recens," otherwise, the patient may receive five to ten times the dose intended, or alternatively, only one-tenth to one-fifth of such dose. The term "Ext.," when applied to glands is ambiguous, and should be avoided.

Further, these products, with one exception, are not official, and there are no generally recognised standards. Thus, each manufacturer devises his own processes of preparation, and possibly some method of standardisation. In these circumstances, a prescription without specification of the maker's name may result in a much stronger, or weaker, or wholly useless product being dispensed.

The undernoted list shows the relationship between the desiccated and fresh gland adopted by Parke, Davis & Co. :—

ONE part of desiccated substance is equivalent to :

FIVE parts of fresh substance in the case of Anterior Lobe, Pituitary ; Corpus Luteum ; Pituitary Body, whole gland, Suprarenal Substance ; Thyroid Gland.

SIX parts in the case of Ovarian Residue ; Ovarian Substance ; Pineal Gland ; Placenta Substance ; Posterior Lobe, Pituitary.

SEVEN parts in the case of Orchic Substance.

EIGHT parts in the case of Mammary Substance and Thymus Gland.

TEN parts in the case of Parathyroid Substance.

Parke, Davis & Company's preparations of the above are, as a rule, labelled so that the grainage represents the amount of desiccated material present. The principal exception to this rule is thyroid, which they, for their European business, label in terms of the fresh gland, the corresponding amount of desiccated substance being also shown. The dose of thyroid was originally based on the fresh gland, and as this dosage is still employed by the majority of medical practitioners it has been retained in order to avoid the risk of over-dosage.

LIST OF GLAND PRODUCTS.

In response to requests from medical men, we have produced a number of formulas of mixed glands, particulars of the composition of which are given on this and the three pages which follow.

No recommendation is offered with these beyond the tentative suggestions made throughout the book, and physicians must themselves be judges as to the applicability of any given formula in particular cases.

THYROID.

THYROID GLANDS, DESICCATED, U.S.P. From the thyroid glands of healthy animals used for human food. Standardised to contain not less than 0.3% of iodine in organic combination. Each grain is equivalent to about 5 grains of fresh gland.

Supplied in the following forms :

The desiccated powder in bottles containing 1 ounce (28 gm.).

COMPRESSED TABLETS, representing $\frac{1}{4}$, $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, $2\frac{1}{2}$, 3, 5, or 10 grains (0.016, 0.032, 0.065, 0.1, 0.13, 0.16, 0.2, 0.325, or 0.65 gm.) of fresh gland (or one-fifth those amounts of desiccated), in bottles of 100, 500 or 1,000.

CHOCOLATE-COATED TABLETS, representing 5 or 10 grains (0.325 or 0.65 gm.) of fresh gland (i.e., 1 or 2 grains of desiccated), in bottles of 100 or 1,000.

THYRAFER TABLETS [Desiccated Thyroid, $\frac{1}{2}$ grain (0.032 gm.), Desiccated Suprarenal, 2 grains (0.13 gm.), Bland Pill, 1 grain (0.065 gm.)], in bottles of 25 and 100.

Thyroid gland is also an ingredient of **SUPRARENAL COMPOUND TABLETS**, **TETRA-GLANDULAR TABLETS**, **THYORCHIC COMPOUND TABLETS**, and **THYROVARIAN COMPOUND TABLETS**.

THYROPROTEIN. A highly purified concentrated extract of thyroid glands from healthy animals, standardised to contain 0.33% of iodine in organic combination.

Supplied in the form of compressed tablets containing, respectively, $\frac{1}{50}$, $\frac{1}{25}$ or $\frac{1}{10}$ grain (0.0013, 0.0026 or 0.0065 gm.) of Thyroprotein, in bottles of 50, and in 1 c.c. ampoules containing the solution of $\frac{1}{50}$ grain (0.0013 gm.), in boxes of 6 or 12.

PARATHYROID.

PARATHYROID GLANDS, DESICCATED.

Supplied in the form of compressed tablets containing $\frac{1}{10}$ grain (0.0065 gm.) or $\frac{1}{20}$ grain (0.003 gm.) of the desiccated substance (equivalent to ten times those amounts of fresh gland), in bottles of 25 or 100.

PARATHYROID AND CALCIUM TABLETS [Desiccated Parathyroid Gland, $\frac{1}{40}$ grain (0.0015 gm.) ; Calcium Lactate, 5 grains (0.325 gm.)], in bottles of 25 or 100.

Parathyroid Gland is also an ingredient of **TETRA-GLANDULAR TABLETS**.

SUPRARENAL.

SUPRARENAL GLANDS, DESICCATED, U.S.P. Represents the entire gland, the cortical as well as the medullary portion, differing in this respect from Adrenalin. Each grain is equivalent to 5 grains of fresh gland.

Supplied in the following forms :

The desiccated powder in bottles containing 1 ounce (28 gm.).

COMPRESSED TABLETS containing 2 grains (0.13 gm.) of the desiccated gland, in bottles of 25 or 100.

CAPSULES containing 2 grains (0.13 gm.) of the desiccated gland, in bottles of 25 or 100.

SUPRARENAL COMPOUND TABLETS [Desiccated Suprarenal Gland, 1 grain (0.065 gm.); Desiccated Pituitary Substance, 1 grain (0.065 gm.); Desiccated Thyroid Gland, $\frac{1}{2}$ grain (0.032 gm.)], in bottles of 25 or 100.

TETRAGLANDULAR TABLETS [Desiccated Suprarenal Gland, $\frac{3}{4}$ grain (0.05 gm.); Desiccated Pituitary Gland, $\frac{1}{3}$ grain (0.02 gm.); Desiccated Thyroid Gland, $\frac{1}{3}$ grain (0.02 gm.); Desiccated Parathyroid Gland, $\frac{1}{40}$ grain (0.0015 gm.)], in bottles of 25 or 50.

Suprarenal Gland is also an ingredient of **ORCHIC COMPOUND TABLETS, OVARIAN COMPOUND TABLETS, THYORCHIC COMPOUND TABLETS, THYRAFER TABLETS, and THYROVARIAN COMPOUND TABLETS.**

ADRENALIN. The pressor principle of the medullary or interstitial portion of the suprarenal gland. Physiologically standardised.

Supplied in fine crystalline powder in vials containing 1 grain (0.065 gm.); as **ADRENALIN CHLORIDE SOLUTION**, 1 in 1,000, in bottles containing 1 ounce (28 c.c.) or 10 c.c., and in ampoules containing 0.5 c.c. (boxes of 6 or 12); also as **ADRENALIN CHLORIDE SOLUTION**, 1 in 10,000, in ampoules of 1 c.c. (boxes of 6 or 12). (For other forms and combinations, *see* catalogue.)

PITUITARY.

ANTERIOR LOBE OF THE PITUITARY BODY.

Supplied in the following forms :

COMPRESSED TABLETS, representing $2\frac{1}{2}$ grains or 5 grains (0.16 or 0.325 gm.) of the desiccated substance (equivalent to five times those amounts of fresh substance), in bottles of 25 or 100.

ANTUITRIN (soluble extract) in 1 c.c. ampoules (boxes of 6).

Anterior Pituitary is also an ingredient of **ORCHIC COMPOUND TABLETS.**

POSTERIOR LOBE OF THE PITUITARY BODY.

Supplied in the following forms :

TABLETS, representing 0.2 gm. (3 grains) of fresh substance [equivalent to 0.03 gm. ($\frac{1}{2}$ grain) of desiccated substance], in tubes of 25.

PITUITRIN (soluble extract), physiologically standardised, in ampoules of 0.5 c.c. (boxes of 6 or 12) or 1 c.c. (boxes of 6).

PITUITARY SUBSTANCE, WHOLE GLAND (anterior and posterior lobes),
DESICCATED.

Supplied in the form of COMPRESSED TABLETS representing 2 grains (0.13 gm.) of fresh whole gland [equivalent to 2/5 grain (0.025 gm.) of desiccated substance], in bottles of 25 or 100.

Pituitary Substance is also an ingredient of OVARIAN COMPOUND TABLETS, SUPRARENAL COMPOUND TABLETS, and TETRAGLANDULAR TABLETS.

OVARIAN PREPARATIONS.

CORPORA LUTEA, DESICCATED. From the corpora lutea of cattle and swine (mostly pregnant). Each grain of the desiccated powder is equivalent to 5 grains of fresh substance.

Supplied in the following forms :

The desiccated powder in bottles containing 1 ounce (28 gm.).

CHOCOLATE-COATED TABLETS containing 2 grains (0.13 gm.) of the desiccated substance, in bottles of 25 or 100.

CAPSULES containing 5 grains (0.325 gm.) of the desiccated substance, in bottles of 25 or 100.

AMPOULES containing 1 c.c. of the soluble extract [equivalent to 3 grains (0.2 gm.) of the desiccated powder], in boxes of 6.

OVARIAN SUBSTANCE, DESICCATED. From entire ovaries of pregnant cattle. One grain of the desiccated powder represents 6 grains of fresh gland.

Supplied in the following forms :

CHOCOLATE-COATED TABLETS containing 1 or 5 grains (0.065 or 0.325 gm.) of the desiccated substance, in bottles of 100. The 5-grain tablets are also supplied in bottles of 25.

AMPOULES containing 1 c.c. of the soluble extract [representing 5 grains (0.325 gm.) of the desiccated powder], in boxes of 12.

OVARIAN COMPOUND TABLETS [Desiccated Ovarian Substance, 2 grains (0.13 gm.) ; Desiccated Suprarenal Gland, 1 grain (0.065 gm.) ; Desiccated Pituitary Substance, 1 grain (0.065 gm.)], in bottles of 25 or 100.

THYROVARIAN COMPOUND TABLETS [Desiccated Ovarian Substance, 3 grains (0.2 gm.) ; Desiccated Suprarenal Substance, 1 grain (0.065 gm.) ; Desiccated Thyroid, $\frac{1}{2}$ grain (0.032 gm.)], in bottles of 25 or 100.

OVARIAN RESIDUE, DESICCATED. This preparation represents only what remains of the ovaries after removal of the ripe corpora lutea. Each grain of the desiccated powder is equivalent to 6 grains of fresh ovarian tissue.

Supplied in the following forms :

The desiccated powder in bottles containing 1 ounce (28 gm.).

TABLETS containing 5 grains (0.325 gm.) of the desiccated substance, in bottles of 25 or 50.

AMPOULES containing 1 c.c. of the soluble extract, in boxes of 12.

TESTES.

ORCHIC SUBSTANCE, DESICCATED. From the testicles of animals.

Supplied in the following forms :

CHOCOLATE-COATED TABLETS containing 5 grains (0.325 gm.) of the desiccated substance [equivalent to 35 grains (2.26 gm.) of the fresh gland], in bottles of 25 or 100.

ORCHIC COMPOUND TABLETS [Desiccated Orchic Substance, 3 grains (0.2 gm.) ; Desiccated Anterior Pituitary, 1 grain (0.065 gm.) ; Desiccated Suprarenal Gland, 1 grain (0.065 gm.)], in bottles of 25 or 100.

THYORCHIC COMPOUND TABLETS [Desiccated Orchic Substance, 3 grains (0.2 gm.) ; Desiccated Suprarenal Substance, 1 grain (0.065 gm.) ; Desiccated Thyroid, $\frac{1}{2}$ grain (0.032 gm.)], in bottles of 25 or 100.

PLACENTA.

PLACENTA SUBSTANCE, DESICCATED. From the placenta of cows.

Supplied in chocolate-coated tablets containing 5 grains (0.325 gm.) of the desiccated substance [equivalent to 30 grains (2 gm.) of fresh placenta], in bottles of 25 or 100.

MAMMARY GLAND.

MAMMARY SUBSTANCE, DESICCATED. Contains portions of all the elements of the mammary gland from young and adult cattle.

Supplied in chocolate-coated tablets containing 5 grains (0.325 gm.) of the desiccated substance [equivalent to 40 grains (2.6 gm.) of fresh gland], in bottles of 25 or 100.

PINEAL.

PINEAL GLAND, DESICCATED. From absolutely fresh pineal glands of young cattle.

Supplied in the form of tablets containing $\frac{1}{10}$ grain (0.0065 gm.) of desiccated pineal gland substance [equivalent to $\frac{3}{5}$ grain (0.038 gm.) of fresh gland], in bottles of 25 or 100.

Supplied in the form of tablets containing :

$\frac{1}{10}$ grain (0.0065 gm.) of desiccated pineal gland substance [equivalent to $\frac{3}{5}$ grain (0.038 gm.) of fresh gland], in bottles of 25 or 100.

THYMUS.

THYMUS GLANDS, DESICCATED. Each grain represents 8 grains of fresh thymus gland.

Supplied in the following forms :

The desiccated powder in bottles containing 1 ounce (28 gm.).

CHOCOLATE-COATED TABLETS containing 2 grains (0.13 gm.) of the desiccated gland, in bottles of 25 or 100.

PROTEIN SENSITIZATION.

It is now established that the entrance of proteins into the body may, under certain conditions, produce either a local or a general reaction, depending on the mode of introduction and the quantity introduced. These allergic phenomena, as they have been called, are exhibited locally if an injection be made intradermally or if the protein substance be massaged into a scarified area of the skin. If instilled in the eye or applied to the nasal mucous membrane, the foreign material causes congestion and irritation of those tissues, as in hay fever. Subcutaneous injection is followed by local or systemic symptoms, depending on whether the quantity of protein is small or great, whereas intravenous, intraperitoneal or intradural injections produce constitutional disturbances. The mildness or severity of the symptoms depends not only on the quantity of protein and the avenue of entrance but also on the sensitiveness of the patient.

Idiosyncrasy.

Individual idiosyncrasy to proteins has been termed sensitization or hypersensitization, a condition which may be related to a great variety of protein substances, not all of them foods. Eggs, milk, fish, shell-fish, wheat, barley, oats, orris root, feathers, epidermal material from dogs, cats and horses, the proteins of pollen and bacteria, and many other substances have been found capable of producing symptoms of sensitization. The various proteins of egg have, for example, been found to be the cause of eczema, asthma, and gastro-intestinal disturbances, the disease varying with different individuals.

Freeman records cases of "toxic idiopathy" excited by material from the horse, cat, rabbit, goat, feathers, etc., by bites of insects, bacterial infection, and even the presence of intestinal worms; also by the taking of milk, egg, honey, apples, horse-meat, rabbit, and various cereals and pulses. (*Lancet*, 1920, II, 229.)

Etiology.

In explanation of protein sensitization, many theories have been advanced, practically all of which are based on the belief that the susceptible person has at some time received a sensitizing amount of the foreign protein, and that the homologous protein, given after a certain interval, produces recognizable symptoms. It is considered necessary that both the sensitizing and the provocative dose should enter the body in such a way as to be subject to parenteral digestion—for instance, by injection or inhalation. Cases of sensitization in which there is no history of a previous injection are explained by the fact that protein substances may enter the blood by way of the digestive tract unchanged, if they are present in excessive amount, or if there are gastro-intestinal abnormalities.

Reference has already been made to the hereditary tendency which is found to exist in certain cases of sensitization. Whole families have been found to possess an idiosyncrasy to a given protein or to several proteins, the kind varying with the different members. In other instances, asthma, urticaria and hay fever have been present in the same family. It is interesting to note that sensitization has been passed from donor to recipient in cases of blood transfusion, and also from a nursing mother to her child.

Hay Fever.

Hay fever is produced in sensitized individuals by the inhalation of pollen, and was the first disease to be definitely attributed to protein sensitization.

In another section of this book the question of sensitization to the pollen of grasses is discussed in detail. The prophylactic treatment suggested was introduced by Noon (*Lancet*, 1911, I, 1572) and elaborated by Freeman (*Ibid*, II, 814). It is important to note that many sufferers from hay fever also show food idiosyncrasies, and in no other disease are protein skin tests of greater importance than in hay fever.

When an infection is engrafted on a pollinosis, and the patient becomes sensitized to both proteins, not only a suitable pollen extract but a bacterial vaccine corresponding to the infection is indicated. In the treatment of other diseases, as well as hay fever, the possible presence of bacterial sensitization should never be overlooked. The patient may also be sensitized to foods and to animal material, in addition to pollen.

A form of vaso-motor rhinitis, caused by proteins other than those of pollen, and presenting a symptom-complex similar to hay fever, may occur at any time during the year, its appearance not being confined to the seasons when pollination takes place. In many perennial cases of so-called "hay fever" the symptoms are due to epidermal material from horses, fowls, or other animals, as well as the ordinary house dust, and these symptoms may be aggravated by irritant vapours and temperature changes.

Asthma.

It is generally recognized that a large number of cases of asthma are attributable to protein sensitization. The well-known fact that injections of horse serum in asthmatic individuals are attended by considerably more risk than in normal persons bears out this explanation. This knowledge places the etiology and the treatment of asthma on a rational basis.

I. C. Walker reports (*Boston Med. and Surg. Journ.*, 179, 288, 1918) 400 cases of asthma studied with regard to foreign proteins as the cause. Forty-eight per cent. of the cases gave positive skin tests. When the patients were classified according to the age at which the first attack of asthma appeared, the following results were obtained: Patients under

2 years, 83 per cent. were positive ; 2 to 5 years, 90 per cent. ; 5 to 10 years, 40 per cent. ; 10 to 15 years, 70 per cent. ; 15 to 35 years, 52 per cent. ; over 50 years, none was sensitive to proteins. It is therefore safe to conclude that the younger the patient when asthma appears, the greater the probability that protein sensitization is the important, if not the sole, etiological factor. With patients over fifty years of age asthma is often of the bronchial type. In other words, such patients are sensitive to bacterial rather than to other proteins, and are said to be suffering from so-called "asthmatic bronchitis." For these cases Mixed Vaccine for Bronchial Asthma (see page 47) may be usefully prescribed.

Walker also found that many persons were susceptible to more than one protein. This was especially true in cases of asthma occurring in infants. Under 2 years, food was by far the most frequently at fault—egg-white, cereals, milk, named in the order of their importance. Later in life—up to 40 years—many patients had become sensitized to bacteria, such as the staphylococcus pyogenes albus and the various types of streptococcus. In half the cases in this series the symptoms were due to the protein of cereals, especially wheat, next in frequency being egg, fish, potato, and casein.

Ramirez (*N.Y. Med. Journ.*, vol. 114, No. 6) found in his cases that the emanations of horse hair and horse dandruff were the most common epidermal cause of bronchial asthma. Of foods, those most commonly at fault were wheat and egg, while next in importance were oats, corn, beef, fish, almond, chicken, walnut, rye, pea, and peanut. Bacterial proteins as causative factors were those of *Streptococcus hæmolyticus*, *Staphylococcus pyogenes aureus*, *Staphylococcus pyogenes albus*, and *Micrococcus catarrhalis*.

Skin Diseases.

Several of the commoner dermatoses have been studied with reference to protein sensitization as a possible cause, and a basis of that nature has been found in a certain proportion of cases of eczema, urticaria, angioneurotic œdema and erythema.

Schloss (*Amer. Journ. Dis. Children*, 19, 433, 1920) reports 19 patients showing some form of proteid sensitization out of 72 cases of urticaria, angioneurotic œdema and erythema multiforme. Fifty-three cases of eczema in patients under 16 months old showed 40 positive to skin tests, while of 24 patients over 16 months 10 were positive.

O'Keefe (*Boston Med. and Surg. Journ.*, 183, 569, 1920) studied 70 patients suffering from infantile eczema, 29 of whom gave a local reaction to one or more foods, egg-white being the commonest cause.

Pagniez and Vallery-Radot (*Medical Press*, May 2, 1923) prescribe a dose of peptone one hour before meals, this method applying more especially to urticaria of digestive origin. Professor Widal, of Paris, at a meeting of the Royal Society of Medicine in London (*Lancet*, June

3, 1923) stated that when the offending substance cannot be clearly identified in cases of urticaria and migraine, protection may be conferred by the administration of ordinary albuminoid substances, such as peptone.

Epilepsy.

In *The Lancet*, April 14, 1923 (p. 741), Mackenzie Wallis, Nicol and Maurice Craig refer to the possibility, long suspected, of food poisons or food susceptibility playing a part in the etiology of certain forms of epilepsy, and describe measures adopted by them for testing the sensitivity of such patients to: (1) egg proteins; (2) meat and fish proteins; (3) milk; (4) vegetable proteins; (5) cereals; and (6) peptone, by observation of their skin reactions to the application of the several tests.

In the event of a positive reaction after such tests the ideal method of treatment is the removal of the offending protein or proteins from the patient's dietary, and if necessary desensitizing the patient by the administration of protein vaccines in small and graduated doses. Peptone given by the mouth is of value in cases reacting to the peptone test.* The best preparation the authors have found is that known as "Medicinal Peptone" in gelatin capsules containing 1 grain. One capsule is given twice a day, *after* food. Some cases react strongly, so that the dose has to be diminished or suspended for some days.

In a series of epileptics tested at Hanwell Mental Hospital it was found that 28 reacted to peptone, 15 to cereals, 15 to fish and meat, 9 to vegetables, 9 to eggs, and 3 to milk. Of 100 other patients and staff, tested as controls, all were negative except 4 cases of dementia præcox, which reacted slightly to peptone.

In some cases in which it has been possible to adjust the diet in accordance with the test reactions, satisfactory results have been obtained without further treatment. Twenty-four patients were treated with peptone orally. In some cases the fits have become less frequent, and in a few there has also been some mental improvement. Two cases became decidedly worse under peptone treatment. After treatment with peptone it was found that some patients no longer reacted to the peptone test.

The diagnosis and treatment by means of skin tests, peptone, and diet applies only to one special type of epilepsy and not to all types, and the secret of success lies in the early diagnosis of the condition and the early application of the treatment.

Ward (*N.Y. Med. Journ.*, vol. 114, No. 6, p. 325) points out that most cases of epilepsy start when the patient is between 2 and 7 years old, at the time when dietary difficulties usually occur. Attacks, moreover, seem to follow hearty meals. He mentions, also, the

* Diagnostic Protein Extract containing Peptone is available in paste form, and may be used for this test.

effectiveness of the fasting method of treating epilepsy, citing this as corroborative evidence of protein sensitization as a cause of the disease, and concludes by saying: "I believe that food is the dominating cause of epilepsy. If epileptics were tested and the foods containing the proteins which reacted positively were eliminated from the diets, we would see a great improvement in the patients, if not an actual cure of the disease."

Other Diseases.

Certain other disease conditions, such as gastro-intestinal disturbances, abdominal pain, mucous colitis, and infantile convulsions, may be due in certain cases to protein sensitization.

Duke (*Archives Int. Med.*, vol. 28, No. 2, 1921, p. 151) gives his experience in several cases, and states that "the gastro-intestinal mucosa may become hypersensitive to an article of food, with the result that the patient experiences severe abdominal pain, often associated with nausea and vomiting, whenever he eats the food to which he is sensitive. Individuals sensitive to uncommon articles of diet, such as roe, lettuce, honey, strawberries, cabbage, tomatoes, etc., usually give a history of occasional attacks of abdominal pain and digestive upsets. They are, as a rule, free from digestive disturbance between attacks. Individuals sensitive to the commoner articles of food, such as milk or eggs, have more frequent attacks of pain, and are often subject to chronic indigestion as well."

Skin Tests.

To determine the presence of protein sensitization, and to establish the identity of the foreign protein, skin tests are employed, based upon the phenomena of local hypersensitiveness. The development of redness and oedema about the point of inoculation is an essential feature of sensitization, and, as the reaction is specific for each protein, it serves to demonstrate the part played by that protein in the causation of a given case of asthma, hay fever, urticaria, or other disease.

The application of protein skin tests may be of great diagnostic value in cases in which demonstrable pathological lesions fail to account for the symptoms, and in deciding that certain lesions are alone responsible the physician should use considerable care. The necessity for this is shown by the report of a case in which, with a high degree of enteroptosis present, all symptoms were greatly ameliorated by abstinence from a certain foreign protein to which the patient was found sensitized. A detailed past and present history of the patient and also of his immediate family, may be of assistance to the physician in making his decision. In one patient, sensitization to horse material

was demonstrated as the cause of his lately developed asthma, the history having indicated that he had received a blood transfusion a short time before from a donor who was thus afflicted.

Three kinds of diagnostic tests have been proposed—ophthalmic, intradermal, cutaneous. The cutaneous test consists in massaging a preparation of the suspected protein into a minute scarification. It is practical, safe, simple and easy to perform. It gives little annoyance or pain to the patient, does not make him ill, and is not too delicate. For these various reasons the cutaneous method has to a great extent superseded the intradermal.

Protein Extracts.

The preparation of Diagnostic Protein Extracts (P., D. & Co.) is begun with the extraction of the original material with water or physiological salt solution, to which has been added a small quantity of a non-irritating antiseptic as a preservative. It is then concentrated, after the addition of glycerin, and mixed with pure boric acid powder in sufficient quantity to make a rather stiff paste. The preparation is standardized in manufacture, so that 1 gramme of the original material makes 1 gramme of completed product.

In protein extracts for diagnosis certain qualities are essential for the ease and effectiveness of their employment. Activity and stability are perhaps the most important of these requisites. In dissolving out the proteins from the primary material, as previously described, no attempt is made to separate the protein from the other soluble elements. This is a point of some significance, as it is believed that the protein in as nearly as possible its native state should give better results than when precipitated and dried, or precipitated and redissolved for purification. The more an antigenic substance is worked with, the more it is exposed to the influence of chemicals, heat, or filtration, the more likely is it to lose its character and depart from the state in which it originally sensitized the patient.

Stability is an essential quality in protein extracts—they should not be subject to early deterioration, which is likely to occur with substances of an albuminous nature. The liquid extracts, unless concentrated in glycerin are extremely unstable; paste and powder extracts are much more permanent. To prove beyond doubt the stability of the diagnostic pastes, experimental lots have been tested six years after manufacture, and found still active.

The pastes adhere to the surface, in any position. The only instruments required for their application are a needle and a few sterilized wooden tooth-picks, as applicators. The time consumed in making tests with the pastes is much shorter than that required for testing with either powder or liquid extracts. All the ingredients of the pastes are soluble in the body fluids, and no irritation attends their application.

Making the Tests.

The forearm or the upper part of the back may be chosen as a field for the application of cutaneous tests. With the diagnostic pastes, as many as twenty-five tests have been performed during an hour, with the patient comfortably seated. This economy of time and effort is a very important matter both to the patient and to the physician.

The cutaneous tests are carried out as follows : The skin of the upper part of the back—or elsewhere, if the physician prefers—is first cleansed thoroughly with soap and water, followed with alcohol, and allowed to dry. A small scarification, or a series of scarifications, as required, are then made with a sterile needle or scarifier. The scarification should be superficial, and should not draw blood. A portion of the paste, the size of a pin's head, is expressed from the tube, taken up on the flat end of a sterile wooden applicator, or blunt scalpel, and rubbed directly into a scarification. If more than one test is being made at the same time, this process is repeated for each suspected protein, using a sterile applicator for each test.

Another method, which is preferred by some authorities, for conducting these tests is to cleanse the forearm, as described above, and to place one drop of 0.4% sodium hydroxide solution on the skin. A small quantity of the protein extract may then be applied by means of a blunt scalpel, and mixed with the soda solution while gently scarifying the skin. The use of the soda solution in this way is said to hasten the appearance of the reaction.

In from five to twenty minutes, if there is sensitization to any of the inoculated proteins it will be manifested by a local reaction. This reaction, which lasts for from half to one hour, consists of a white or pink urticarial weal, usually surrounded by a zone of erythema. The weals vary greatly in size and colour ; the erythema surrounding them is usually of a fairly intense and constant red.

It is always advisable (as a control) to have one or two scarifications into which no protein is massaged, as an unusually sensitive skin may, in some instances, respond with a confusing local reaction merely as a result of the traumatism. For this purpose, a control paste which contains no protein extract is supplied.

The paste should be left on for about thirty minutes, thus giving ample time for the appearance of a possibly delayed reaction. The local signs usually fade and disappear in a few hours.

Peptone paste is a useful additional diagnostic agent, as many cases which react to the protein extracts will also react to peptone. Such a reaction suggests Medicinal Peptone (P., D. & Co.) as a general desensitizer.

Interpreting the Tests.

Observers of wide experience require for a positive test the appearance of a weal not less than half a centimetre ($1/5$ in.) in diameter. When the weal is below that size or is absent, even in the presence of a marked patch of erythema, the test is considered doubtful.

As with some other diagnostic reactions, a negative result is not so definite and reliable as a positive. Sensitization may vary in activity from day to day, or even from hour to hour. A test that is positive to-day may for no apparent reason be negative to-morrow; or, in other cases, an acute attack of the disease caused by protein absorption may result in temporary desensitization and a negative test. For these reasons the physician should not consider a negative test final but should test the patient repeatedly if there is the slightest suspicion of protein hypersusceptibility.

Positive tests, regardless of the normality of the patient, must be interpreted as indications of true protein sensitization. The usual explanation of the absence of general symptoms in these cases is that the in-take of the offending protein is not great enough to exceed the individual's tolerance. Such persons should be regarded as susceptible to protein intoxication and potential victims of hay fever, asthma, urticaria, or other diseases of the same etiological type.

Group Protein Extracts.

While the physician is not restricted to making one test at a time, but may apply half a dozen or more proteins from different tubes in different locations, all at one session, economy of time and patience may be attained by the use of group tests. In addition to the individual tubes (see pages 185, 186), tubes containing from three to six different protein extracts are supplied, so that a single application will enable the physician to exclude all of the proteins represented in the tube, or to assure himself that one or more of them is at fault. If the former, he makes another test with another group of proteins, continuing until he gets a positive reaction. If the latter, he will proceed to make individual tests with each of the proteins represented in the group, or of such individual extracts of foods, etc., as are likely to be involved, applying each to a separate scarification—at one and the same time if so disposed. It is possible that a patient may be sensitive to an extract of a food he has never eaten and is never likely to eat; obviously such sensitization may be ignored.

Necessarily the groups are more or less arbitrary; but they assist the physician greatly in simplifying the diagnosis.

It will obviously not be necessary, in the great majority of cases, to employ the whole series of the group extracts, but the experience of the physician will enable him to select from the following list those

extracts likely to contain the offending protein for the particular case in question. In this connection a knowledge of the habits and environment of the patient will be found most helpful, and the patient's history may sometimes give a useful clue. Just as an asthma occurring throughout the year will not be due to some seasonable article of diet, so an asthma which occurs only at certain seasons will probably not be caused by an everyday food. It should be borne in mind that the epidermal groups should not be omitted, as statistics show that 50% of asthmatic cases can be ascribed to hypersensitiveness to foreign protein, and of these two-thirds can be attributed to animal hairs and feathers. Of the foods, those most commonly associated with asthmatic conditions are oats, wheat, egg albumen, milk, beans, peas, cabbage, almonds, cheese, chicken, rice and tomatoes. On account of its extensive use in toilet preparations, orris root is by no means an uncommon cause.

In view of the fact that pollen, animal hairs, feathers, etc., come into direct contact with the respiratory mucous membrane, whereas foods are subjected to the influence of digestive ferments, it is not surprising that considerably more reliance may be placed on positive reactions to the epidermal proteins, pollen and orris root, than to positive reactions with food proteins.

Even when a case may be known to be definitely bacterial in origin, it may be wise not to omit the skin test, since hypersensitiveness may be a secondary complicating factor. At the same time, it often happens that such patients fail to give definitely positive reactions.

When positive reactions are obtained avoidance of the proteins causing these reactions is obviously indicated. This has been shown to be strikingly successful in the case of the epidermal proteins, namely, hairs and feathers. It is more difficult to avoid pollen and horse material, but desensitization to these substances may, as a rule, be successfully brought about by the hypodermic injection of "Pollaccine" or "Hippaxine," respectively, as detailed elsewhere in this book. Desensitization to food proteins has not reached the stage at which satisfaction can reasonably be anticipated. Experience has shown that the oral administration of Medicinal Peptone (P., D. & Co.) in doses of one to two grains has been attended with considerable success, especially in certain cases of asthma. The dose is given one hour after meals at varying intervals, as the patient's sensitiveness may direct.

Group Protein Extracts.

Supplied in collapsible tubes containing $1\frac{1}{2}$ grammes of a mixture of equal parts of the protein extracts from substances named under the respective group headings.

Group 1, Meats :

Beef.
Lamb.
Pork.
Veal.
Mutton.

Group 2, Egg and Milk :

Cow's milk (all proteins).
Egg (all proteins).
Cheese.
Human milk.

Group 3, Fish :

Codfish.
Haddock.
Halibut.
Herring.
Mackerel.
Smelt.

Group 4, Fish :

Perch.
Pike.
Salmon.
Bluefish.
Shad.
Sole.

Group 5, Fowl :

Chicken.
Duck.
Goose.
Turkey.
Squab.
Guinea-hen.

Group 6, Shellfish :

Clam.
Oyster.
Shrimp.
Scallop.
Lobster.
Crab.

Group 7, Vegetables :

White potato.
Sweet potato.
Beet.
Turnip.
Carrot.

Group 8, Vegetables :

Lima bean.
Navy bean.
String bean.
Peas.
Lentil.

Group 9, Vegetables :

Celery.
Asparagus.
Onion.
Egg-plant.
Radish.
Garlic.

Group 10, Vegetables :

Cabbage.
Cauliflower.
Lettuce.
Spinach.
Parsnip.

Group 11, Vegetables :

Pumpkin.
Squash.
Cucumber.
Sweet peppers.
Tomato.
Rhubarb.

Group 12, Nuts :

Chestnut.
Peanut.
Pecan.
Almond.

Group 13, Nuts :

Black walnut.
Brazil nut.
English walnut.
Hickory nut.
Butternut.

Group 14, Cereal :

Wheat.
Rye.
Buckwheat.

Group 15, Cereal :

Rice.
Oatmeal.
Barley.
Corn (maize).

Group 16, Fruits :

Apple.
Pear.
Prune.
Plum.
Fig.

Group 17, Fruits :

Cantaloup.
Water-melon.
Peach.
Cherry.
Banana.
Pineapple.

Group 18, Fruits :

Orange.
Lemon.
Grapefruit.
Strawberry.
Blackberry.
Raspberry.

Group 19, Beverages :

Coffee.
Tea.
Cocoa.

Group 20, Bacterial :

Colon bacillus.
Gonococcus.
Staphylococcus aureus.
Staphylococcus albus.
Staphylococcus citreus.

Group 21, Bacterial :

Friedländer bacillus.
Micrococcus catarrhalis.
Micrococcus tetragenus.
Pseudodiphtheria bacillus.

Group 22, Bacterial :

Pneumococcus, I, II, III.
Streptococcus (hæmolytic).
Streptococcus (non-hæmolytic).

Group 23, Bacterial :

Typhoid bacillus.
Paratyphoid "A."
Paratyphoid "B."

Group 24, Epidermal :

Hair of cattle.
Hair of cat.
Hair of dog.
Hair of horse.

Group 25, Epidermal :

Hair of rabbit.
Hair of guinea-pig.
Wool of sheep.

Group 26, Epidermal :

Feathers of chicken.
Feathers of duck.
Feathers of goose.

Group 27, Seasonings :

Ginger.
Mustard.
Pepper, Black.
Pepper, Red.
Paprika.
Sage.

Food Protein Extracts.

Supplied in collapsible tubes containing, approximately, 1½ grammes—sufficient for from forty to fifty tests.

101 Almond.	130 Corn (maize).	159 Orange.
102 Apple.	131 Crab.	160 Oyster.
281 Apricot.	132 Cucumber.	161 Parsnip.
103 Asparagus.	133 Duck.	162 Pea.
104 Banana.	134 Egg (all proteins).	163 Peach.
105 Barley.	135 Egg white.	164 Peanut.
106 Bean, Lima.	136 Egg yolk.	165 Pear.
107 Bean, navy.	137 Egg-plant.	166 Pecan.
108 Bean, string.	138 English walnut.	167 Peppers, sweet.
109 Beef.	139 Fig.	168 Perch.
110 Beet.	140 Garlic.	169 Pike.
111 Blackberry.	141 Goose.	170 Pineapple.
112 Black walnut.	142 Grapefruit.	171 Plum.
113 Bluefish.	143 Guinea-hen.	172 Pork.
114 Brazil nut.	144 Haddock.	173 Prune.
115 Buckwheat.	145 Halibut.	174 Potato, sweet.
116 Butternut.	146 Herring.	175 Potato, white.
117 Cabbage.	147 Hickory nut.	176 Pumpkin.
118 Cantaloup.	148 Lamb.	177 Radish.
119 Carrot.	149 Lemon.	178 Raspberry.
120 Cauliflower.	150 Lentil.	179 Rhubarb.
121 Celery.	151 Lettuce.	180 Rice.
122 Cheese.	152 Lobster.	181 Rye.
123 Cherry.	153 Mackerel.	182 Salmon.
124 Chestnut.	154 Milk, cow's (all proteins).	183 Scallop.
125 Chicken.	155 Milk, human.	184 Shad.
126 Clam.	156 Mutton.	185 Shrimp.
127 Cocoa.	157 Oatmeal.	186 Smelt.
128 Codfish.	158 Onion.	187 Sole.
129 Coffee.		188 Spinach.

Food Protein Extracts, *concluded*.

189 Squab.	192 Tea.	196 Veal.
190 Squash.	193 Tomato.	197 Water-melon.
191 Strawberry.	194 Turkey.	198 Wheat.
	195 Turnip.	

Pollen Protein Extracts.

199 Yellow daisy.	203 Artemisia	208 Rye.
200 Ox-eye daisy.	204 Oats.	209 Timothy grass.
201 Golden-rod.	205 Ragweed.	210 Oak.
202 Juniper.	206 Red top.	301 Pine.
	207 Russian thistle.	

Epidermal Protein Extracts.

211 Feathers of chicken.	214 Hair of cattle.	218 Hair of horse.
212 Feathers of duck.	215 Hair of cat.	219 Hair of rabbit.
213 Feathers of goose.	216 Hair of dog.	220 Wool of sheep.
	217 Hair of guinea-pig.	

Miscellaneous Protein Extracts.

231 Ginger.	234 Pepper, Black.	238 Serum, Bovine
232 Mustard.	235 Pepper, Red.	239 Serum, Horse.
233 Orris root.	236 Paprika.	240 Tobacco.
999 Peptone.	237 Sage.	

Bacterial Protein Extracts.

251 Colon bacillus.	260 Staphylococcus albus.
252 Friedländer bacillus.	261 Staphylococcus aureus.
253 Gonococcus.	262 Staphylococcus citreus.
254 Micrococcus catarrhalis.	263 Streptococcus, hæmolytic.
255 Micrococcus tetragenus.	264 Streptococcus, non-hæmolytic.
256 Pneumococcus, type 1.	265 Typhoid bacillus.
257 Pneumococcus, type 2.	266 Paratyphoid bacillus A.
258 Pneumococcus, type 3.	267 Paratyphoid bacillus B.
259 Pseudodiphtheria bacillus.	

100 CONTROL (for diagnostic proteins).

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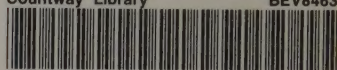
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